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STEREOCHEMICAL STUDIES OF ANTIHISTAMINIC AGENTS

by



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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

FACULTY OF PHARMACY AND PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA

SPRING, 1970

Thesis
1970
280

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Stereochemical Studies of Anti-histaminic Agents", submitted by Robin Robert Ison, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

ABSTRACT

A review of stereochemical studies of antihistaminic agents is given to illustrate the marked stereospecificity of the histamine receptor in its relation to antagonists. In the light of this knowledge, an extended series of molecularly rigid aminoalkene isomers were synthesised and examined for their antihistaminic activities. The structure and configuration of pure isomers were established from spectroscopic data and the most potent derivatives were shown to possess similar spatial arrangements of molecular units and functions. These results are discussed in terms of the possible structural and conformational requirements of histamine antagonists and the likely preferred conformations of a number of more flexible antihistamines in clinical use have been correlated with the stereochemical characteristics of the most active aminoalkenes.

A study of the conformational preferences of histamine itself under close to physiological conditions was carried out aided by PMR spectroscopy. Various analogues of histamine substituted in the terminal N atom or the ethyl side chain were also examined by the PMR method and the present state of knowledge of the histamine-like agonist activities of such derivatives is reviewed.

Finally, attempts were made to introduce the imidazole heterocycle into an antihistaminic structure.

ACKNOWLEDGEMENTS

The author wishes to express sincerest thanks to Dr. A.F. Casy for his unflagging interest, constructive criticism and able supervision during the course of this research.

Special thanks are extended to Drs. R.T. Brittain and R.G.W. Spickett of the Department of Pharmacology, Allen and Hanburys, Ware, England, who evaluated the anti-histaminic activities of numerous compounds cited in this thesis.

The willing co-operation of Dr. N.S. Ham, C.S.I.R.O., Chemical Research Laboratories, Division of Chemical Physics, Clayton, Victoria, Australia, in determining the precise PMR parameters of histamine and its sidechain Me analogues using computerial methods is gratefully acknowledged.

The author also wishes to express sincere thanks to Dr. Michael N.G. James and Mr. Graheme J. Williams of the Department of Biochemistry, University of Alberta, for permission to publish some of their preliminary X-ray crystallographic data on Brompheniramine maleate.

Grateful thanks are also extended to the Medical Research Council of Canada for financial support throughout the course of this study and to Eli Lilly and Company, Montreal, for the supply of a sample of Pyronil phosphate.

Thanks are also due to Mrs. Sining Li for running many routine IR spectra and to Mr. Glenn Bigam of the Department of Chemistry, University of Alberta, for determining several 100 MHz PMR spectra.

Finally, a special thanks to my wife, Susan, for her professional advice on the layout of the thesis and for her expert typing of the whole manuscript.

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ABBREVIATIONS AND NOMENCLATURE

No attempt has been made to follow a rigorous system of organic nomenclature since structural formulae have been provided for all the compounds referred to in this thesis.

The following abbreviations have been used throughout the main body of the text:

CNS	Central nervous system
IR	Infra-red
UV	Ultra-violet
PMR	Proton magnetic resonance
Me	Methyl
<u>t</u> -Bu	<u>t</u> -Butyl
ppm	Parts per million
TMS	Tetramethylsilane
DSS	Sodium 2,2-dimethyl-silapentane-5-sulphonate
GLC	Gas liquid chromatography

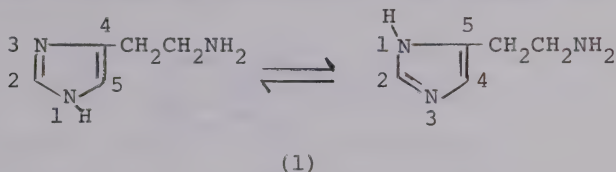
In most cases, any drugs mentioned are described under their proprietary names as indicated by an initial capital letter.

CHAPTER 1

INTRODUCTION

INTRODUCTION

Histamine (1) first appeared in the literature in 1907, after its synthesis by Vogt and Windraus, only three years before its isolation as a natural product from ergot (Barger and Dale 1910a, b; Kutscher 1910). During the

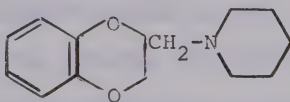


next two decades histamine was identified as a natural constituent of many body tissues and fluids (Barger and Dale 1911; Abel and Kubota 1919; Best et al. 1927) and Grant and Lewis (1924) showed that its cellular release depended upon either injurious stimuli or antigen-antibody reactions. The latter phenomenon is now known to produce anaphylactic shock or troublesome allergic conditions such as hay fever, asthma and urticaria (Burger 1963).

Dale and Laidlow (1910) carried out the first pharmacological investigation of histamine and discovered its potent stimulation of the contraction of smooth muscle; after this initial study, a great volume and variety of biological research revealed other physiological actions of histamine including the relaxation of the smooth muscle of the arterioles leading to decreased blood pressure, greater

permeability of the capillary walls producing oedema, and increased activity of the gastric secretory glands (Barlow 1964).

Counteraction of one of the main biological effects of histamine was first demonstrated by use of 2(1-piperidino-methyl)1,4-benzodioxane (2) which protected guinea pigs from



(2)

bronchial spasms induced by a histamine spray (Bovet et al. 1937). This compound was the forerunner of a profusion of active molecules termed 'antihistamines' which suppress many of the symptoms of allergic conditions. These compounds appear to act as competitive antagonists of histamine by occupying the receptor sites of the effector cells without eliciting a response (Gilman and Goodman 1965). Antihistamines may thus be classified as having high 'affinities' but negligible 'intrinsic activities' according to the theory of Ariëns (1964). However, the gastric secretory action of histamine is unaffected (Trendelenburg 1960; Ash and Schild 1966) by these compounds.

The classic concept of a stereospecific "lock-and-key" drug:receptor interaction mediating a biological response was postulated by Paul Erlich (1913) after Langley

(1906; 1909) had recognised the presence in muscular tissue of a 'receptive substance' to curare and nicotine. Although Ehrlich's theory was a great scientific breakthrough which laid the foundations of medicinal chemistry philosophy it is now realized that the idea is an oversimplification considering the problems of multistructure complexes and conformational changes in macromolecules (Mautner 1969, and references there cited).

Since histamine has several well defined effects it may be assumed that the biological response is via a receptor or receptors. Pharmacological characterisation of histamine receptors indicates at least two distinct types; the H_1 receptor is implicated in histamine induced spasm of the guinea pig ileum and is selectively antagonised by antihistamines (Ash and Schild 1966). The other receptor type or types are involved in the action of histamine on gastric acid secretion, the rat uterus and mammalian heart (Paton 1970).

In this thesis, unless otherwise stated, the term 'receptor' will refer to the H_1 type for histamine as all our potential antihistamines were tested for their ability to antagonise histamine induced spasms of the guinea pig ileum.

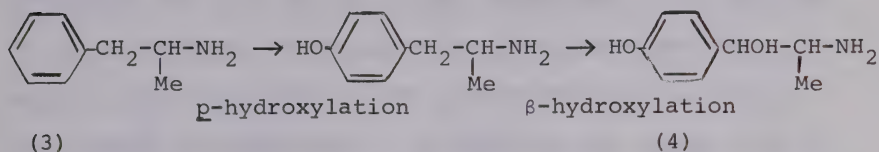
Indirect knowledge of receptor characteristics may be gained by study of the stereochemistry of the agonists with which they interact and the antagonists by which they

are blocked, assuming a complementary 'fit' between the receptor and the drug or agent forming the complex. In the absence of direct methods, and inspite of the limitations of the "lock-and-key" approach, this remains one of the most successful avenues for the design and understanding of more effective or selective agents.

When receptors may be shown to discriminate between stereoisomers, some knowledge may be obtained about the geometrical disposition of the active sites of the receptor. However, all structure:activity studies are complicated by factors other than receptor events such as differences in drug absorption, distribution, metabolism, uptake at storage sites and excretion and many of these processes may be stereoselective. Although enantiomorphs do not differ in physical properties in symmetric media, within asymmetric environments their properties can differ greatly. Physiological media are generally asymmetric so that pronounced differences can occur in the absorption, transport and metabolism of enantiomers within a biological matrix and such phenomena have been observed. A few selected examples will now be mentioned.

Steric factors can influence the penetration of natural membranes and it has been found that R-amino acids are absorbed more rapidly in the small intestine than the corresponding S-enantiomers (Beckett 1963). Radiochemical study of the distribution of (+) and (-)- α -methyldopa in the rat has shown that the (-)-isomer attained higher concentrations

in most organs in accord with the specific hypotensive activity of the laevo enantiomorph (Sjoerdsma and Udenfriend 1961). A careful study of the two-step metabolic pathway for amphetamine (3) was very revealing in



that only the dextro isomer suffered the second hydroxylation process to yield the metabolite (4). (Anagnoste and Goldstein 1965). This may correlate with the more significant pharmacological properties of the dextro antipode (Galland and Gunne 1967).

In contrast, geometrical isomers normally differ in physical and sometimes chemical properties (irrespective of the media) whether they are of the ring or alkenic type (see Figure 1) and the relative amounts reaching the

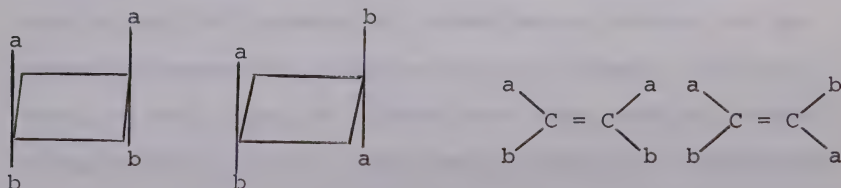


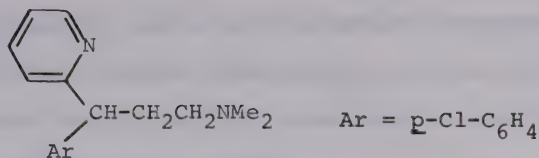
Figure 1. Geometrical isomerism in cyclic or alkenic structures.

receptors may differ significantly under the influence of the preceding physiological processes. These complicating factors can be minimised by the use of isolated tissue preparations for testing rather than whole animals.

Alkenic cis:trans isomers are relatively rigid in structure and this can be a great advantage in the delineation of receptor characteristics. Cyclic geometrical isomers are more flexible and conformational equilibria must always be considered. In addition the latter type of isomerism is often associated with optical activity because of the lack of a plane of symmetry (Eliehl 1962) and this can further complicate the interpretation of structure: activity data.

Histamine itself is formally a symmetric agonist but there is the possibility of an 'asymmetric preferred conformation' (see later) interacting with the receptor (Kier 1968). Some antagonists may also interact in preferred conformations. A number of antihistamines provide possibility for geometrical isomerism and others are inherently asymmetric producing optical isomers. The pure forms of both types of isomers have been examined pharmacologically in several instances and activity differences have been shown.

Thus, chlorpheniramine (5) has been resolved and the enantiomorphs tested. The dextro form was 12 times more active than the laevo in ability to protect guinea



(5)

pigs against the effects of intravenously administered histamine and a histamine aerosol (Govier and Roth 1958). The absolute configuration of the dextro isomer has been established by chemical correlative methods (Hite and Shafi'ee 1969) to be S according to the nomenclature and sequence rule of Cahn, Ingold and Prelog (1956).

Green (1953a) has similarly reported significant activity differences in the optical isomers of two 3,3-dithienylalkenylamines (6). From Table I it can be seen that the dextro antipode is the more potent antihistamine.



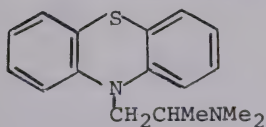
TABLE I

Antihistaminic Activity Ratios of the Optical Antipodes of Two 3,3-Dithienylalkenylamines

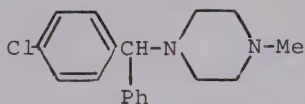
Compound	(+):(±) activity ratio	(-):(±) activity ratio
6a	1.41	0.60
6b	1.33	0.81

The clinically useful antihistamine, Promethazine (7), has also been resolved (Borsy et al. 1959a) but the dextro and laevo isomers had the same antihistaminic and CNS activity (Borsy et al. 1959b).

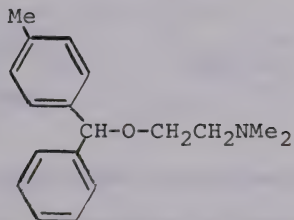
A number of racemic antihistamines including Chlorcyclizine (8), Toladryl (9) and Phenindamine (10)



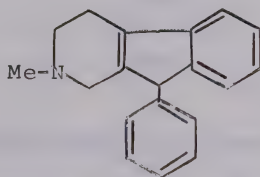
(7)



(8)



(9)

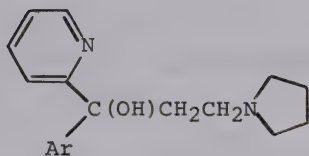


(10)

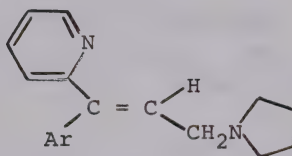
have high activity but there are no reports in the literature on the individual activities of optical isomers.

Large antihistamine activity differences are known amongst several classes of compounds where the possibility of geometrical isomerism exists. Adamson and coworkers (1951) separated the isomers obtained from dehydration of

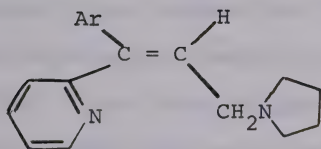
the tertiary alcohol (11) and found that the trans (2-pyridyl/CH₂N) compound (12) was 80 times more potent than the corresponding cis isomer (13) in ability



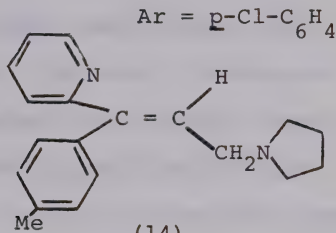
(11)



(12)



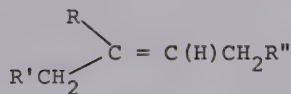
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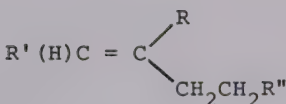
(14)

to antagonise histamine-induced spasm of guinea pig ileum. Extension of their studies (Green 1953b; Adamson et al. 1957; 1958) lead to the introduction of Triprolidine (14) as an antihistamine drug.

A series of antihistaminic 4-aminobutenes have been reported (15, 16 and 17) and the diphenyl but-2-ene (15a; R = R' = Ph) and but-1-ene (16a; R = R' = Ph) had significant activity whereas the potency of the 3-methyl but-2-ene derivative (17a; R = R' = Ph) was only moderate (Frey et al. 1950). However the compounds were not satisfactorily characterised in regard either to double



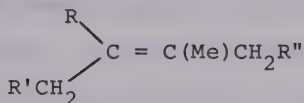
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(16)

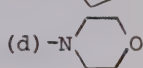
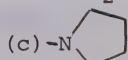
R = Aryl,
thienyl
R' = Aryl,
cyclohexyl

R'' = (a) NMe₂

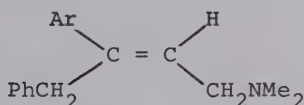


(17)

(b) NEt₂



bond position or configuration. Casy and Pocha (1967) re-investigated the reactions aided by PMR spectroscopy and several pure geometrical isomers were isolated. Subsequent pharmacological testing of these isomers and several others from a later study suggested that the disposition of functions about the double bond in cis (Ar/H)1,2-diarylbut-2-enes



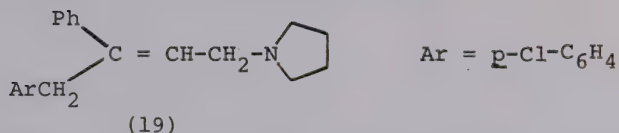
(18)

(a) Ar = Ph

(b) Ar = p-MeO-C₆H₄

(18) was optimal for antihistaminic activity (Casy and Parulkar 1969).

Nearly two decades earlier more than fifty 1,2-diarylbut-2-enes were screened at the Lilly Research Laboratories and the potent antihistaminic drug 'Pyronil' (19) was discovered. The isomeric purity and configuration of the drug



have never been reported although the compound is described as a 4-amino-1,2-diarylbut-2-ene (Anderson et al. 1952), and not a but-1-ene.

From all the preceding discussion it is clear that the histamine receptor, at least in its relation to antagonists, displays stereospecificity. Thus a further study of the stereochemical features of blocking agents may well provide data about histamine receptor features and the nature of its interaction with agonists and antagonists.

CHAPTER 2

AIMS AND OBJECTS

AIMS AND OBJECTS

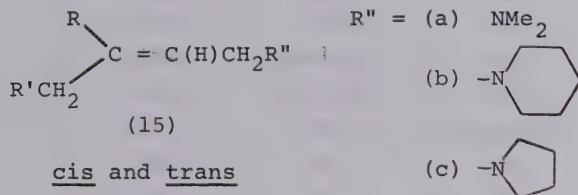
It is evident from the preceding introduction that the activities of several different types of compounds with antihistaminic properties are affected by their molecular shapes. It is therefore of interest to search for further examples amongst the stereoisomers of antihistaminic derivatives and to ascertain whether or not common stereochemical features exist for compounds with this type of pharmacological activity. If a specific arrangement of molecular units and functions does, in fact, prove to be associated with a high order of antihistaminic potency, information will be provided regarding the preferred 'active' conformations of known antihistamine agents which do not formally exist in stereoisomeric modifications. This conformation may not necessarily correspond with the energetically preferred arrangements and allowance must be made for conformational changes as a result of drug-receptor interactions.

The amino-propene and amino-butene antihistaminic types are intrinsically rigid about the carbon-carbon double bond in their structures and from thermodynamic considerations it is most unlikely that their configuration will change after formation of the complex with the receptor. It was hence thought desirable to investigate an extended series of basic propene and butene isomers to observe general structure:activity relationships and to

identify the optimum geometry (if any) necessary for significant antagonist activity against histamine. If this was possible some of the more flexible antihistamines would then be studied in relation to the aminoalkene configurations to search for possible analogies resulting from likely preferred conformations.

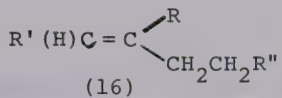
Accordingly, investigation of the following structural series was proposed:

(i) 4-aminobut-2-enes

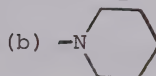


Compound	R	R'
15a	Ph	Ph
15a	<u>t</u> -Bu	Ph
15a	<u>o</u> -Me-C ₆ H ₄	Ph
15a	2-pyridyl	Ph
15a	Ph	2-pyridyl
15b	Ph	Ph
15c	Ph	Ph
15c	Ph	<u>p</u> -Cl-C ₆ H ₄

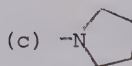
(ii) 4-aminobut-1-enes



R'' = (a) NMe₂

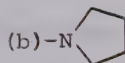
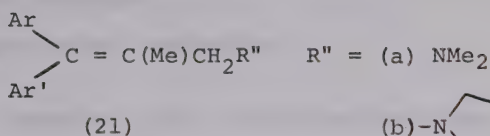
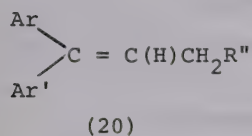


cis and trans

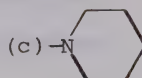


Compound	R	R'
16a	Ph	Ph
16a	<u>t</u> -Bu	Ph
16a	<u>o</u> -Me-C ₆ H ₄	Ph
16a	2-pyridyl	Ph
16a	Ph	2-pyridyl
16b	Ph	Ph
16c	Ph	Ph
16c	Ph	<u>p</u> -Cl-C ₆ H ₄

(iii) 3-aminopropenes



cis and trans (where applicable)



Compound	Ar	Ar'
20a	Ph	2-pyridyl
20a	<u>o</u> -Me-C ₆ H ₄	2-pyridyl
20a	Ph	Ph
20b	<u>p</u> -Me-C ₆ H ₄	2-pyridyl
21a	Ph	2-pyridyl
21a	Ph	Ph
21b	Ph	2-pyridyl
21c	Ph	2-pyridyl

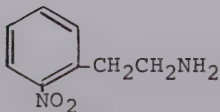
Each series involves

- (i) Syntheses
- (ii) Separation of isomers
- (iii) Assignment of configuration using various physical methods
- (iv) Pharmacological evaluation

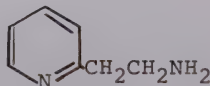
In the event, numerous other structures were prepared during the course of this work; the reasons for making them are discussed at appropriate points in the text.

It was also felt that a study of the conformational preferences of histamine itself under close to physiological conditions was desirable to complement the work on the antagonists. Included in this section are various analogues of histamine substituted in the terminal N atom or the ethyl side chain.

Finally, it was noted that the o-nitrophenyl and 2-pyridyl analogues (22 and 23) of histamine have negligible



(22)



(23)

agonist effects on the guinea pig ileum (Jones, 1966) and yet the phenyl and 2-pyridyl moieties are common aromatic features of many potent antihistamines. Therefore another aim of the work was to introduce an imidazole nucleus into a molecular structure having potential antihistaminic properties.

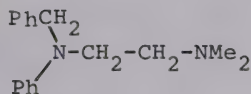
CHAPTER 3

4-AMINOBUTENES AND ANALOGOUS COMPOUNDS

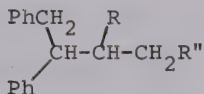
RESULTS AND DISCUSSION

(i) HISTORICAL INTRODUCTION

Just 20 years ago, the antihistaminic activity of 4-aminobutenes was fortuitously discovered by Frey and co-workers (1950) at the Geigy Laboratories. The group were investigating analogues of the known antihistamine, Antergan (24), in which the nitrogen atom was isosterically



(24)

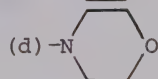
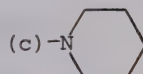


(25)

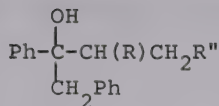
R = H, Me

R'' = (a) NMe₂

(b) NEt₂



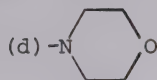
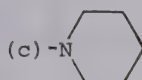
replaced by a saturated carbon. It had been decided to prepare a series of aminobutanes (25) in the hope of finding increased pharmacological activity and the penultimate stage of the synthetic scheme involved acid catalysed dehydration of the tertiary alcohols (26). However, double-bond positions in the aminoalkene products were not rigorously established inspite of the possibility of loss of water in either of two ways to form but-2 (15 and 17) or but-1-enes (16 and 27). In addition, no configurational assignments were made of the cis and trans butene isomers.



R = H, Me

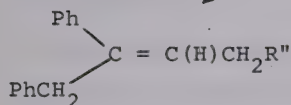
R'' = (a) NMe₂

(b) NEt₂

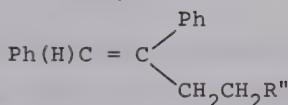


(26; R = H)

(-H₂O) (-H₂O)



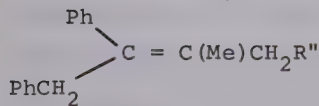
(15; R = R' = Ph)



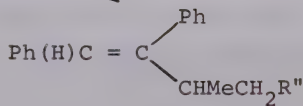
(16; R = R' = Ph)

(26; R = Me)

(-H₂O) (-H₂O)



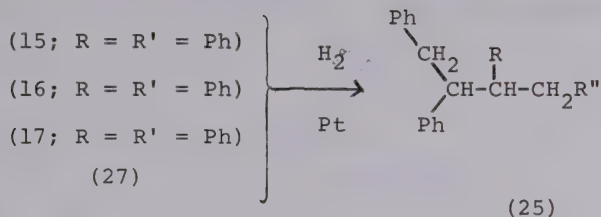
(17; R = R' = Ph)



(27)

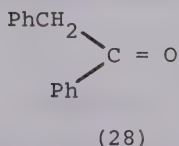
These deficiencies had no effect on the last step of the synthetic route (catalytic hydrogenation to the required aminobutane) because both the cis and trans compounds of

each positional isomer gave the same reduced product (25).



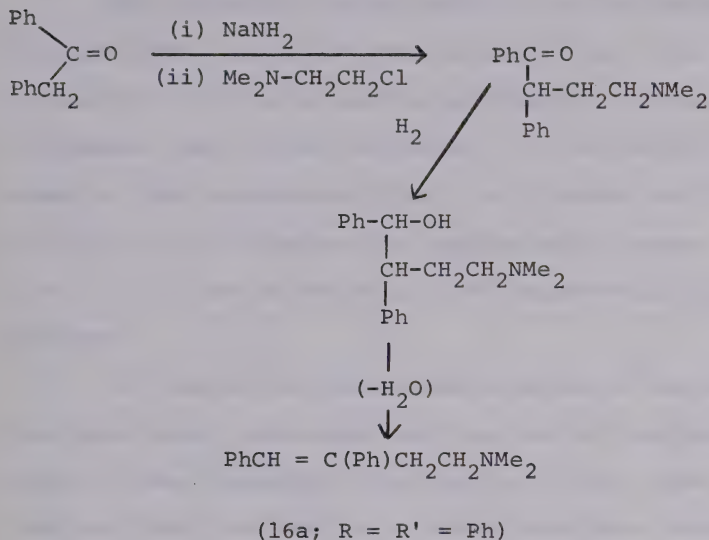
However, the Swiss group reported the aminobutene intermediates to be but-2-enes (15 and 17) on two points of evidence:

1. The 4-aminobutene derived from acid catalysed elimination of the 1,2-diphenylbutanol (26a; R = H) yielded



desoxybenzoin (28) after oxidative cleavage with potassium permanganate. It was noted that the latter product could only be produced by fission of the double bond in the but-2-ene.

2. An authentic but-1-ene (16a; R = R' = Ph) prepared by an unambiguous route from desoxybenzoin (28) had distinctly different physical properties and was less active as an antihistamine than the assumed but-2-ene (15a; R = R' = Ph)



(see Table II) obtained from the tertiary alcohol (26a, R = H).

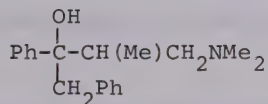
Table II

Comparative Antihistaminic Activities of Some Aminobutenes
and Aminobutanes

<u>Compound</u>	<u>Dosage equivalent in effect to</u> <u>1γ of Antergan</u>
	(1 mg = 1000γ)
25a (R = H)	53.0γ
(15a; R = R' = Ph)	3.4γ
(16a; R = R' = Ph)	12.7γ
(17a; R = R' = Ph)	11.1γ
(15b; R = R' = Ph)	3.3γ

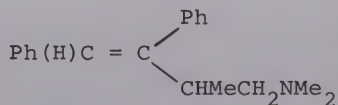
The biological tests conducted by the Geigy workers produced some unexpected results and it was found that the precursor aminobutenes were significantly stronger anti-histamines than the aminobutanes (25) (see Table II). For example, the aminobutane (25a; R = H) showed only a low activity (53.0%) whereas the corresponding butene (15a; R = R' = Ph) had an activity (3.4%) approaching that of Antergan.

In view of the inconclusive nature of the double bond positional assignment and the lack of configurational data on these compounds, Casy and his group (1966, 1967, 1968 and 1969) decided to reinvestigate the elimination reactions aided by modern physical methods. The 3-methyl alcohol (26a; R = Me) which yielded the least active anti-histaminic compound (17a; R = R' = Ph) was initially studied and PMR examination of the products of acid catalysed



(26; R = Me)

dehydration showed, in contradiction to the Swiss workers report, that the but-1-enes (27a) were exclusively produced



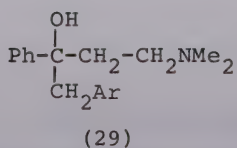
cis and trans

(27a)

(Casy et al. 1966). The spectrum of the total base product showed two closely overlapping vinylic singlets, two NMe_2 singlets and the sec Me proton signal was composed of two overlapping doublets. The duplication of each signal was due to the presence of cis and trans isomers and integration of the signals indicated the correct number of protons for a but-1-ene formulation. The complete absence of any singlet attributable to a tert 3-methyl group ($=\text{CMe}$) characteristic of a but-2-ene confirmed the sole formation of but-1-ene products (27a) under the prevailing reaction conditions.

The cis and trans but-1-ene isomers of (27a) were later separated by fractional crystallisation of the hydrochloride salts and configurations were inferred on the basis of PMR characteristics of isomeric pairs. Differences in the NMe_2 and 3-Me signals were used and comparisons were made with the appropriate resonance positions of a number of authentic cis and trans α -substituted stilbenes (Casy et al. 1968).

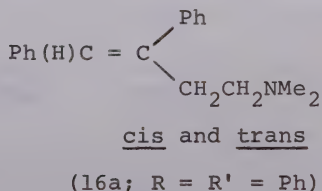
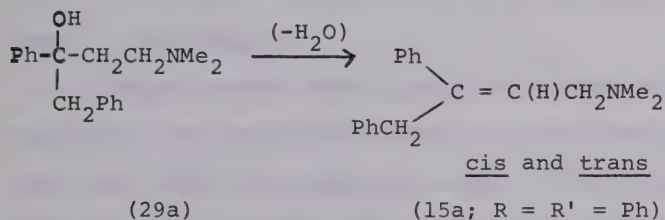
The overall study was continued and dehydration of the nor-analogues (29) under the same reaction conditions



- Ar = (a) Ph
(b) $p\text{-Me-C}_6\text{H}_4$
(c) 2-pyridyl

was reinvestigated to examine the validity of Frey and coworkers' (1950) but-2-ene structural assignments (Casy and Pocha 1967). Elimination of the tertiary alcohol (29a) was of particular importance as the aminoalkene product or products were known to be of comparable potency to Antergan (see Table II, compound 15a; R = R' = Ph).

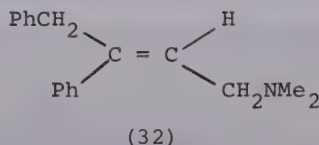
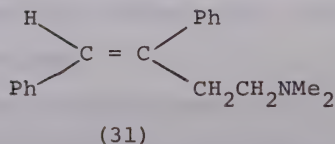
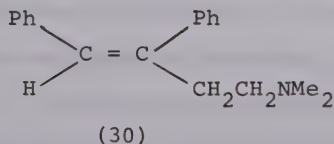
Just as before, loss of water could theoretically occur in two ways to produce either but-2 or but-1-ene products. Each of these products could exist in the cis and trans forms so that a total of four isomers was expected.



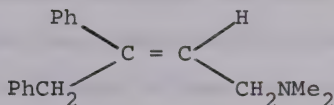
The PMR spectrum of the total base product derived from the butanol (29a) after a three hour reflux period with an acetic-hydrochloric acid mixture indicated it to be a

mixture of all four possible butenes (cis and trans 15a and 16a; R = R' = Ph). The vinylic signals consisted of two singlets and two triplets, characteristic of the but-1 and but-2-enes respectively; in addition, four closely spaced singlets were evident in the dimethylamino resonance region of the spectrum. Isomeric separations were attempted by fractional crystallisation of the butene mixtures after acidification with ethanolic hydrogen chloride and a large number of crops were obtained. The varying compositions of each sample were deduced from UV and PMR spectroscopic evidence and the arguments for structural assignments are fully discussed during the extended aminobutene study described at a later point in this thesis (see p. 34 et seq.).

Three isomers were finally separated as pure hydrochlorides from the mother liquor and they were the cis but-1-ene (30), the trans but-1-ene (31) and the trans (H/Ph) but-2-ene (32). The initial crop in one experiment



was revealed as a ternary mixture of the two but-1-enes (30 and 31) and the cis (H/Ph) but-2-ene (33) and its composition was found to be virtually identical to a

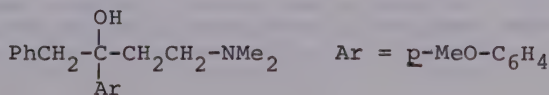


(33)

sample of the assumed but-2-ene (15a; R = R' = Ph) obtained by Frey and coworkers (1950) in their earlier study. The Geigy workers kindly supplied a sample of this, their most active antihistaminic butene, and a PMR spectrum in CDCl₃ immediately disclosed its three component formulation.

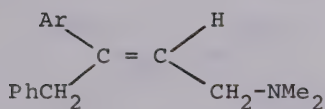
A pure sample of the cis (H/Ph) but-2-ene (33) hydrochloride could not be obtained and no pure isomers were isolated from the four-component mixture of butenes derived from the p-tolylaminoalcohol (29b). A solitary but-1-ene (16a; R = Ph; R' = 2-pyridyl) was obtained from a base catalysed elimination of the 2-pyridyl alcohol (29c) after acid catalysed elimination had failed.

Study of the dehydration of 4-dimethylamino-2-p-methoxyphenyl-1-phenylbutan-2-ol (34) in a similar manner yielded pure samples of all four aminoalkene hydrochlorides

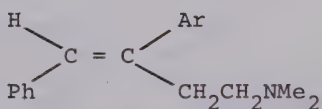


(34)

(Casy and Parulkar 1969). The antihistaminic potencies of these isomers together with the previously prepared 3-methylaminobutenes (27a) and the nor-aminobutenes including the ternary mixture identical to the most active Geigy sample, were measured for their ability to antagonise the histamine-induced contraction of guinea-pig ileum. Wide differences in activity amongst aminobutene isomers indicated that antagonism of histamine is stereoselective in nature. The 3-methylaminobutenes (27a) had only moderate activity but certain of the nor-aminobutenes were extremely potent. The cis (H/Ph) but-2-ene (35) and the trans but-1-ene (36) were far more active than their corresponding geometrical isomers and the duration of action of compound (35) was particularly



(35)

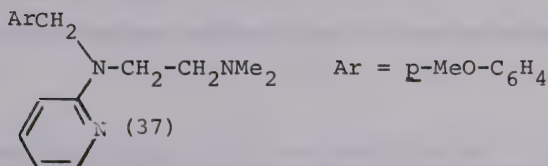


Ar = p-MeO-C₆H₄ (36)

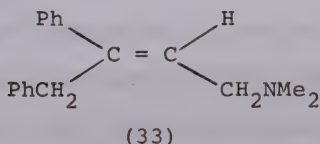
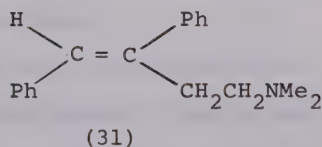
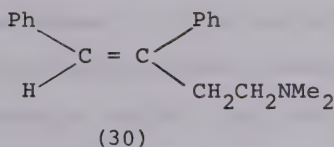
prolonged. However, its pA₂* value was 6.94 which indicated considerably less activity than that possessed by

* The value of pA₂ is the logarithm of the reciprocal of the concentration of antagonist which necessitates doubling the concentration of agonist in order to keep the effect constant (Barlow 1964). This pharmacological parameter was originally conceived by Schild (1947). All the pA₂ values quoted in this thesis were evaluated after the drug had been in contact with the tissue for a 2 minute period.

Mepyramine (37) (pA_2 8.67), the standard antihistamine used as the control in the pharmacological testing. The most highly



active diphenylaminobutene proved to be the ternary mixture identical to the Geigy groups' sample which had been wrongly allocated a but-2-ene structure (Frey et al. 1950). It had a pA_2 value of 9.4 comparable with those of highly active antihistaminic agents (Barlow 1964). The mixture was composed of the cis and trans but-1-enes (30 and 31) and the cis (H/Ph) but-2-ene (33) and since both but-1-enes



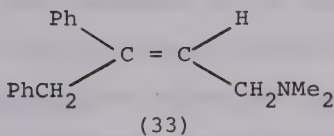
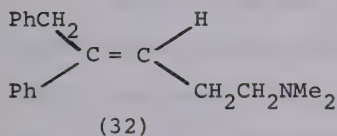
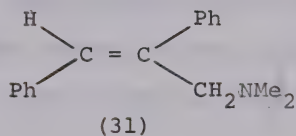
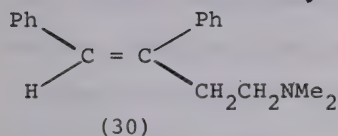
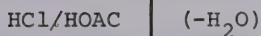
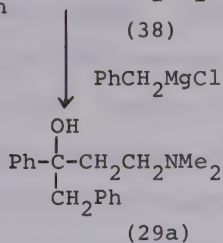
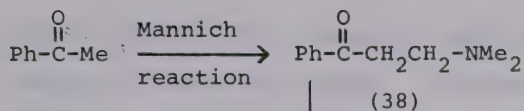
were much less active than the mixture it was deduced (assuming synergism is not operative in the mixture) that the cis (H/Ph) but-2-ene (33) must be an extremely active antihistamine.

It was therefore considered important to attempt to isolate this compound in pure form and to prepare other pure cis (H/Ph) but-2-enes to confirm that the disposition of pharmacophoric groups about the double bond in these molecules are optimal for histamine antagonist action.

(ii) ISOLATION OF CIS (H/Ph)-4-DIMETHYLAMINO-1,2-DIPHENYL-BUT-2-ENE (33) AS A HYDROBROMIDE

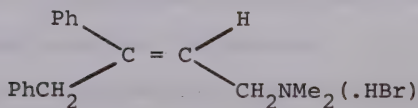
Following the unsuccessful attempt to separate the cis (H/Ph) but-2-ene (33) as a pure hydrochloride salt (Casy and Pocha 1967) it was decided to repeat the synthesis and to acidify the total alkenic product instead with hydrogen bromide. It was hoped that subsequent fractional crystallisation would lead to isolation of the required but-2-ene isomer (33) as the hydrobromide.

The reaction route commenced with the preparation of the Mannich ketone (38) from acetophenone, dimethylamine hydrochloride and paraformaldehyde in the classic manner. The ketone was then treated with ethereal benzylmagnesium chloride to form the tertiary alcohol (29a). Acid catalysed elimination of the latter using an acetic-hydrochloric acid mixture and a four hour reflux period produced all four aminobutene isomers (30, 31, 32 and 33) as shown by the PMR spectrum of the total base. Acidification of the mixture with ethanolic hydrogen bromide yielded a large number of



HBr

fractional crystallisation

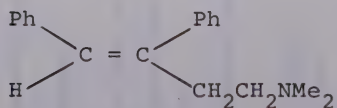


(33)

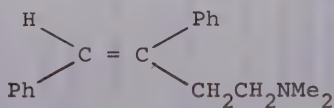
crystal crops after successive additions of ether over a period of about two months. Numerous recrystallisations were carried out and PMR spectra of selected crops were run to determine their isomeric compositions (see later for configurational inferences by PMR and UV spectroscopy). Eventually a crude mixture of the required cis (H/Ph) but-2-ene (33) hydrobromide contaminated with a trace amount of the cis but-1-ene (30) was obtained. These two isomers were identified by the characteristic chemical shifts and multiplicities of the various proton signals in their structures which were known from Casy and Pochas' (1967) earlier work.

Several further recrystallisations of the crude product from ethanol/ether finally yielded the pure cis (H/Ph) but-2-ene (33) hydrobromide as colourless needles, m.p. 179-180°. The PMR and UV characteristics of this compound and the other three isomers (30, 31 and 32) obtained by Casy and Pocha (1967) are shown in Table III. The assignment of configurations to the four isomers is based upon these spectral parameters.

In the case of the but-1-enes (30 and 31) molecular



(30)



(31)

TABLE III

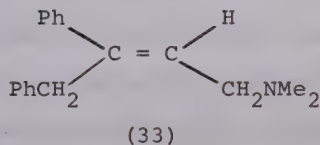
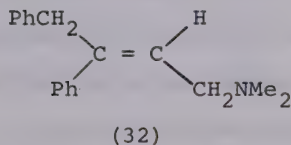
SPECTRAL CHARACTERISTICS OF 1,2-DIPHENYL-4-DIMETHYLAMINO-BUT-1- AND BUT-2-ENES

Sample	Compound Number (s) in text	Chemical shifts ^a				λ_{\max} (ϵ) ^e
		C-1 vinyl ^b	C-3 vinyl ^c	NMe ₂ ^b	Others	
<u>cis</u> (H/Ph)but-2-ene .HBr	(33)	-	378	166 ^f (J5)	CH ₂ Ph 240 ^d NCH ₂ CH: 231 ^f (J7)	241 (11500)
<u>trans</u> (H/Ph)but-2-ene .HCl	(32)	-	358	160	CH ₂ Ph 225 ^d NCH ₂ CH: 213 ^f (J7)	end absorption
base from above hydrochloride	(32)	-	337	129	CH ₂ Ph 221 ^d NCH ₂ CH: 172 ^f (J7)	-
<u>cis</u> -but-1-ene.HCl	(30)	401	-	168	NCH ₂ CH ₂ 188 ^d	255 (11270)
base from above hydrochloride	(30)	390	-	132	NCH ₂ CH ₂ 234 ^d	-
<u>trans</u> but-1-ene.HCl	(31)	416	-	162	NCH ₂ CH ₂ 192 " 186 ^g	263 (16800)
Total base elimination product	(30) (31) (32) (33)	406 ^d 389 ^d	367 338	135,131 129,127	NCH ₂ CH ₂ 234 ^d CH ₂ Ph 219 ^d	-

^a Chemical shifts in Hz from TMS (internal standard)^d Broad singlet.^e Solvent water; λ_{\max} is wavelength in m μ ; extinction coefficient (ϵ) in parenthesis.^b Singlet.^f Doublet.^g Broad signals of A₂B₂ pattern.^c Triplet (J7).

models indicate greater overall planarity in the trans isomer (31) than in the corresponding cis compound (30). In consequence, the vinylic proton of the trans isomer lies more in the plane of the aromatic rings and should thus be deshielded to a greater extent than the corresponding cis proton (Bovey and Johnson 1958). Furthermore, the absorption maximum of the phenyl double bond chromophore should be more intense and at longer wavelength in the more planar trans isomer. Hence, the but-1-ene isomer (31) with the lower field vinylic singlet (416 Hz*) and the more intense UV absorption (λ_{max} 263; ϵ 16800) was assigned the trans and the other but-1-ene (30) (vinylic chemical shift 401 Hz; λ_{max} 255; ϵ 11270) the cis configuration.

Comparison of molecular models of the but-2-enes (32 and 33) indicates that the double bond and 2-phenyl



* It should be noted all chemical shifts expressed in Hz from TMS have been recorded at 60 MHz unless otherwise stated. Hz have been used in this thesis so that shifts are described by whole numbers, unlike the ppm (δ) and tau (τ) systems which are expressed to two decimal places. The Hz nomenclature, however, does suffer the disadvantage of denotation of lower field by higher Hz value.

group may only be coplanar in the cis (H/Ph) isomer (33) because in the trans isomer (32) the same conformation is markedly unfavoured by orthohydrogen-aminomethyl non-bonded interactions. In consequence, the but-2-ene (33) with the lower field vinylic triplet (378 Hz) and the styrenoid absorption band (λ_{max} 241; ϵ 11500) was assigned the cis (H/Ph) but-2-ene configuration. The trans (H/Ph) compound (32) displayed a higher field vinylic signal (358 Hz) and its UV spectrum showed only end absorption which confirmed twisting of the 2-phenyl group out of the plane of the double bond as a result of steric interaction with the adjacent methyleneamino group.

(iii) PHARMACOLOGICAL EVALUATION OF THE 4-DIMETHYLAMINO-1, 2-DIPHENYLBUTENE ISOMERS (30, 31, 32 AND 33)

Thus, the required cis (H/Ph) but-2-ene (33) was isolated and characterised as the hydrobromide salt and its antihistaminic potency was measured by its ability to antagonize the histamine-induced contraction of the guinea-pig ileum. The other three dimethylamino isomers (30, 31 and 32) had been tested previously (Casy and Parulkar 1969) and were found to have feeble activity. However, a sample of the trans (H/Ph) but-2-ene (32) and a ternary mixture were retested at the same time as the cis (H/Ph) but-2-ene so that semi-quantitative activity comparisons could be made. Drs. R.T. Brittain and R.G.W. Spickett of Allen and Hanburys,

TABLE IV

INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM

BY 4-DIMETHYLAMINO BUTENES

Sample	Compound Number in text	Conc. $\mu\text{g/ml}$	Percentage inhibition at time (in min.)									
			3	6	9	12	15	18	21	24	27	
<u>cis</u> (H/Ph)but-2-ene.HBr	(33)	0.01	89	84	79	62	52	28	-	-	-	-
<u>trans</u> (H/Ph)but-2-ene.HCl	(32)	0.10	87	62	45	20	-	-	-	-	-	-
ternary mixture (.HCl's) of <u>cis</u> and <u>trans</u> but-1-enes (<u>major</u>) and <u>cis</u> (H/Ph)but-2- ene (minor)	(30) (31) (33)	0.10	90	71	62	56	50	29	8	-	-	-
Mepyramine standard	(37)	0.001	81	50	20	5	-	-	-	-	-	-

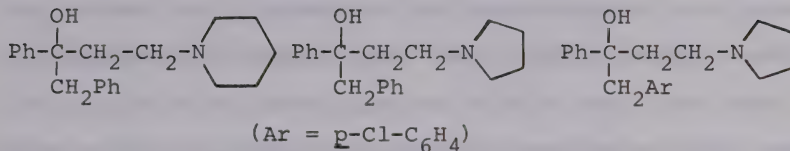
N.B. In the table, a dash denotes discontinuation of experimental observation.

Ware, England, kindly arranged these tests and were also responsible for all the other antihistaminic evaluations cited in this thesis.

The data obtained are shown in Table IV and the cis (H/Ph) but-2-ene (33) had significantly greater potency and duration of action than the trans analogue (32), bearing in mind the tenfold solution concentration difference of the two compounds. In addition, the cis isomer (33) possessed greater activity than the ternary mixture which was of similar composition to the previously mentioned three component mixture (see page 29) already known to be strongly antihistaminic and having a pA_2 of 9.4 (Casy and Parulkar 1969). These results confirmed previous suspicions that the cis (H/Ph) but-2-ene (33) is an extremely potent antihistamine and most importantly, that it is the most active 4-dimethylamino-1,2-diphenylbutene isomer.

(iv) PREPARATION OF FURTHER 4-AMINO-1,2-DIARYLBUTENE
GEOMETRICAL ISOMERS

It was thought necessary to synthesize further examples of 4-amino-1,2-arylbutenes to extend knowledge of the antihistaminic activities of the cis and trans alkenic isomers of these compounds. In this regard it was decided to prepare and dehydrate the alcohols shown below (26c; R = H; 39 and 40).

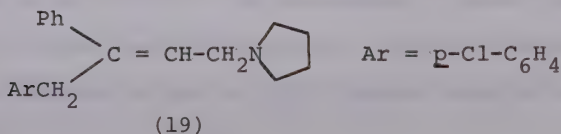


The N-piperidino (26c; R = H) and N-pyrrolidino alcohols (39) were prepared by reaction of the appropriate Mannich ketones with benzylmagnesium chloride and the



resulting carbinols were dehydrated to form aminobutenes containing tertiary amino groups well known in many biologically active compounds.

The tertiary alcohol (40) was synthesized from p-chlorobenzylmagnesium chloride and the aminoketone (42)



and formed the intermediate for preparation of the potent antihistamine, Pyronil (19). The isomeric purity, double bond position and configuration of this drug have never been reported although Anderson and coworkers (1952) have described it as a 4-amino-1,2-diarylbut-2-ene. It was hence considered particularly interesting to reinvestigate the elimination of this alcohol (40) and to attempt isolation of the aminobutene products. If pure isomers were obtained they would be compared physically and spectroscopically with a commercial sample of Pyronil to ascertain the true composition of this drug.

Acid Catalysed Elimination of 1,2-Diphenyl-4-(1-piperidino)butan-2-ol

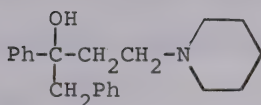
The alcohol (26c; R = H) was dehydrated using an acetic-hydrochloric acid mixture and a 2.5 hour reflux period which allows for equilibration (Casy et al. 1966). The PMR spectrum of the total base product indicated the presence of all four aminobutene isomers (41, 42, 43 and 44) which were identified by the previously discussed method of Casy and Pocha (1967). The approximate proportions of each isomer in the quaternary mixture were estimated from the integral values of the vinylic proton signals and were as follows:

trans but-1-ene (44) 55%

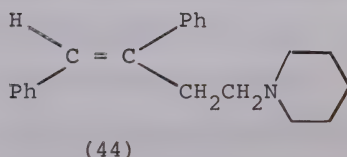
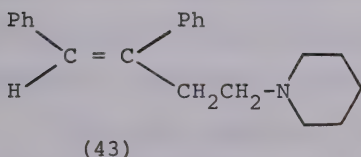
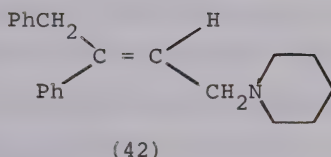
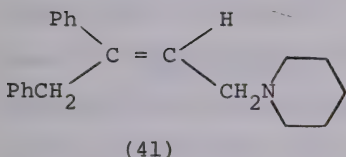
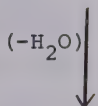
cis but-2-ene (41) 25%

cis but-1-ene (43) 15%

trans but-2-ene (42) 5%



(26c; R = H)



Acidification with ethanolic hydrogen chloride and successive additions of ether followed by cooling at 0° produced a large number of aminobutene hydrochloride crops. The first two collections from the fractional crystallisation gave crystalline samples with sharp and equal melting points (248-249°). PMR spectra in CDCl₃ identified them as

the isomerically pure cis (H/Ph) but-2-ene (41) hydrochloride exhibiting a characteristic vinylic triplet at 382 and benzylic and methyleneamino signals at 237 and 226 Hz (see Table V). These parameters agreed well with the corresponding figures of 378, 240 and 231 Hz respectively (see Table III), for the 4-dimethylamino cis (H/Ph) but-2-ene (33) as did the UV absorption maximum of 241 m μ (cf. compound 33, λ_{max} 241 m μ).

In the meantime, PMR spectra were used to observe the progressing fractional crystallisation and a number of mixtures enriched with the trans but-1-ene (44) began to emerge until eventually two crops of the pure trans but-1-ene (44) hydrochloride m.p. 195 $^{\circ}$, were collected. Continued workup of the crystallisation also provided the isomerically pure cis but-1-ene (43) hydrochloride m.p. 160-161 $^{\circ}$, but a sample of the minor trans but-2-ene (42) (only 5% abundant in the total mixture) could not be obtained even after conversion of the mother liquor to a hydrobromide mixture.

Frey and coworkers (1950) at the Geigy laboratories (see start of Chapter 3) had previously carried out an acid catalysed elimination of the same carbinol (26c ; R=H) and they isolated an aminobutene hydrochloride. The melting point of this product was 246-249 $^{\circ}$ which is very close to that of the authentic cis (H/Ph) but-2-ene (41) hydrochloride described above, which crystallised out first from

our own reaction mixture. It therefore seems probable that this Geigy product was the isomerically pure cis but-2-ene.

The spectral parameters of the pure isomers (41, 43 and 44) are given in Table V and subsequent biological testing revealed the cis (H/Ph) but-2-ene (41) as the most potent antihistamine of the three compounds (see Table VI), having a pA_2 value of 8.76 comparable to those of antihistaminics in clinical use e.g. chlorpheniramine (5) 8.82 and Chlorcyclazine (8) 8.63 (Barlow 1964). However, further tests on the cis (H/Ph) but-2-ene (41) revealed undesirable CNS depressant properties.

Concurrent sedative side effects of a number of antihistamines are well known and Hansson and Schmitterlöw (1961) effectively eliminated this unwanted property in the antihistamine, Promethazine (7), by formation of the quaternary ethylene chlorhydrin derivative, Aprobit (45).

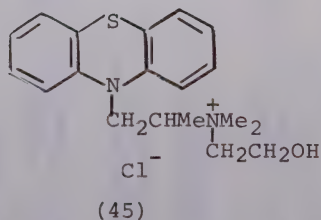
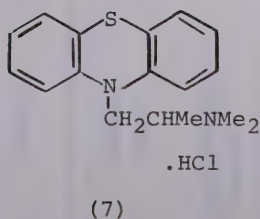






TABLE V

SPECTRAL CHARACTERISTICS OF FURTHER 4-AMINO-1,2-DIARYLBUTENE ISOMERS

Elimination Substrate	Sample	Compound Number(s) in text	Chemical shifts ^{a,b}			$\lambda_{\max}^{(\epsilon)}$ ^f
			C-1 vinyl ^c	C-3 vinyl ^c	Others	
$\text{Ph}-\underset{\text{CH}_2\text{Ph}}{\overset{\text{OH}}{\text{C}}}-\text{CH}_2\text{CH}_2-\text{N}$  (26c; R=H)	total base	(41) (42) (43) (44)	408 391	371 341	-	-
"	cis(H/Ph)but- 2-ene.HCl	(41)	-	382	CH ₂ Ph 237 ^e NCH ₂ CH: 226 ^g (J8)	241 (15400)
"	cis but-1-ene .HCl	(43)	395	-	-	255 (17100)
"	trans but-1- ene.HCl	(44)	406	-	-	263 (20000)
$\text{Ph}-\underset{\text{CH}_2\text{Ph}}{\overset{\text{OH}}{\text{C}}}-\text{CH}_2\text{CH}_2-\text{N}$  (39)	total base	(47) (48) (49) (50)	403 386	367.5 337	-	-
"	cis(H/Ph)but- 2-ene.HCl	(47)	-	377	CH ₂ Ph 238 ^e NCH ₂ CH: 229 ^e	240 (12700)
"	trans but-1- ene.HCl	(50)	415	-	-	261 (20400)
$\text{Ph}-\underset{\text{Ar}}{\overset{\text{OH}}{\text{C}}}-\text{CH}_2\text{CH}_2-\text{N}$  (40) Ar=p-Cl-C ₆ H ₄	total base	(51) (52) (53) (54)	403.5 388	371 341	-	-

Continued

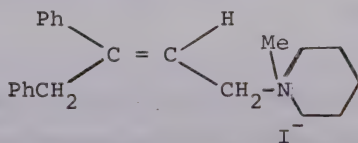
TABLE V (Continued)

OH Ar	C-1 vinyl ^c	C-3 vinyl ^d	Others	$\lambda_{\max}(\epsilon)^f$
Ph-C-CH ₂ CH ₂ -N Ar				
				
cis(H/Ph)but- 2-ene.HCl	(51)	-	-	241 (12500)
Ar= <u>P</u> -Cl-C ₆ H ₄ (40)		368 ^h		
"				
base from above hydrochloride	(51)	-	CH ₂ Ph 231 ^e NCH ₂ CH: 1989 (J7)	-
"				
trans(H/Ph)but- 2-ene.HBr	(52)	-	CH ₂ Ph 220 ^e NCH ₂ CH: c.215 ⁱ	end absorption
"				
cis but-1-ene .HBr	(53)	397.5	-	266 (15800)
"				
trans but-1- ene.HBr	(54)	407.5	NCH ₂ CH ₂ 194 ^j	268 (19200)

- a Chemical shifts in Hz from TMS (internal standard) at an operating frequency of 60 MHz; solvent CDCl₃, coupling constants (J) in Hz.
- b Only distinct and unambiguous absorptions quoted owing to masking by the piperidino and pyrrolidino ring methylene absorptions.
- c Singlet.
- d Triplet (J7).
- e Broad singlet.
- f Solvent water; λ_{\max} is wavelength in mμ; extinction coefficient (ε) shown in parenthesis.
- g Doublet.
- h Ill resolved spectrum in DMSO-d₆ (TMS). The compound is insoluble in D₂O and CDCl₃.
- i Partially submerged doublet.
- j Centre of broad multiplet.

Their idea was to increase the hydrophilicity of the drug so that it was insufficiently lipophilic to cross the hypothetical 'blood-brain barrier' into the CNS. They prepared a series of quaternary derivatives of Promethazine (7), and pharmacological testing showed that Aprobit (45) retained the antihistaminic activity of its parent (7) but lost all its sedative action. The other quaternary derivatives also showed reduced sedative properties but lost all or most of their antihistaminic activity.

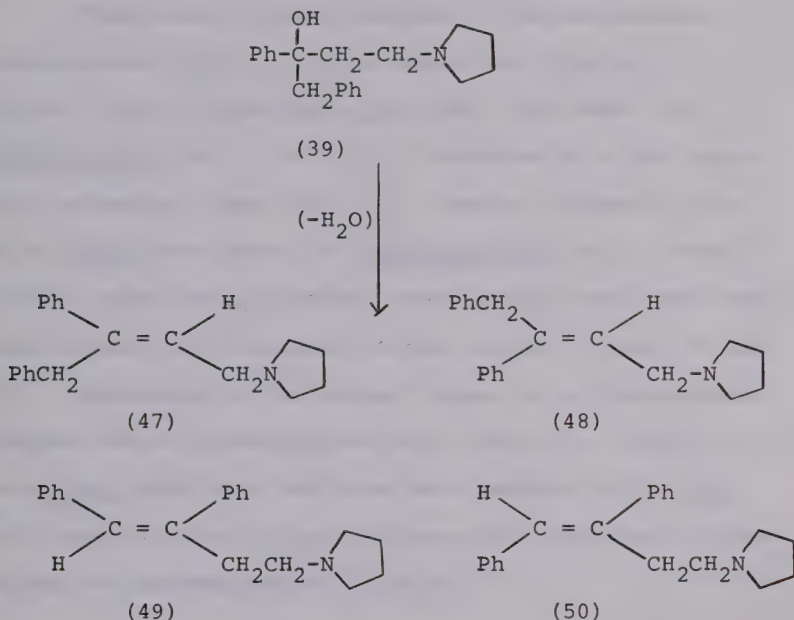
It was therefore decided to prepared the ethylene chlorhydrin quaternary derivative of the cis (H/Ph) but-2-ene (41) in an attempt to remove its undesirable CNS effects. The aminobutene free base was refluxed with ethylene chlorhydrin in benzene for 66 hr. but the resulting gum could not be crystallised. However, the quaternary methiodide (46) was synthesised quite easily and this derivative was submitted for antihistaminic testing.



(46)

Acid Catalysed Elimination of 1,2-Diphenyl-4
-(1-pyrrolidino)butan-2-ol

The carbinol (39) was eliminated under acid-catalysed conditions just as the previously described



pipéridino analogue (26c; R = H). PMR examination of the product showed formation of all four aminobutene isomers (47, 48, 49 and 50) as evidenced by the presence of two singlets and two triplets in the vinylic region of the spectrum. Examination of the integral values of the vinylic proton signals gave the following approximate proportions of each isomer:

trans but-1-ene (50) 55%

cis but-1-ene (49) 20%

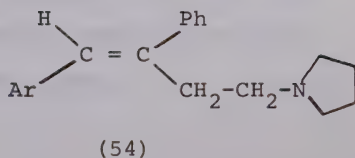
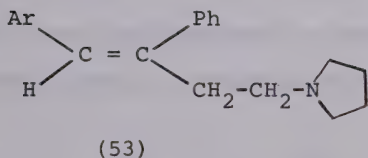
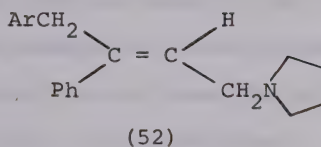
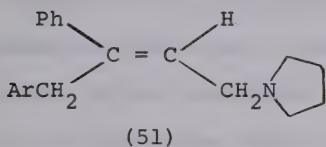
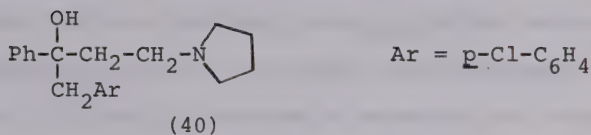
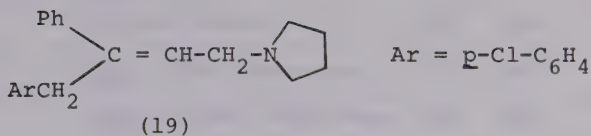
cis but-2-ene (47) 15%

trans but-2-ene (48) 10%

Fractional crystallisation of the aminobutene hydrochloride mixture in the normal way yielded initial crops of the pure cis (H/Ph) but-2-ene (47) hydrochloride, m.p. 198°, with characteristic PMR spectral parameters (see Table V), closely followed by the major trans but-1-ene (50) hydrochloride, m.p. 160-162°. Further crops were collected over several weeks and were mostly irresolvable mixtures of the two but-1-enes (49 and 50). Conversion of the mother liquor to a hydrobromide mixture was no advantage and only led to the isolation of more trans but-1-ene and thus pure samples of the cis but-1-ene (49) and trans but-2-ene (48) could not be obtained for pharmacological testing.

Acid Catalysed Elimination of 1(p-chlorophenyl)-2-phenyl-4-(1-pyrrolidino)butan-2-ol

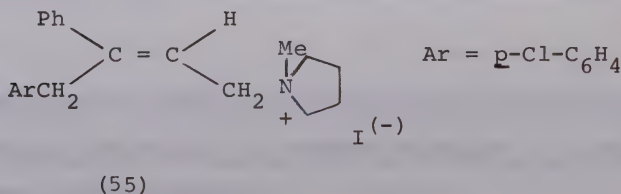
The carbinol (40) precursor of Pyronil (19), a potent antihistamine of unknown configuration (see pages 11 and 12), was dehydrated in the normal way and PMR examination of the total base product revealed the presence



of all four possible aminobutene isomers (51, 52, 53 and 54). The integral values of the four vinylic signals (two triplets and two singlets) showed that the isomeric mixture consisted of the following proportions of each compound:

<u>trans</u> but-1-ene	(54)	45%
<u>cis</u> but-1-ene	(53)	20%
<u>cis</u> (H/Ph) but-2-ene	(51)	20%
<u>trans</u> (H/Ph) but-2-ene	(52)	15%

Acidification of the mixture with ethanolic hydrogen chloride gave initially the cis (H/Ph) but-2-ene (51) hydrochloride, m.p. 227-228°, which agreed with the m.p. (227-228°) previously reported for Pyronil hydrochloride (Patent, 1953a). This strongly suggested that Pyronil is the cis (H/Ph) but-2-ene (51) and the assumption was confirmed by the PMR spectrum of the free base isolated from a commercial sample of Pyronil phosphate, which corresponded exactly to that (see Table V) of the free base derived from (51). The quaternary methiodide derivative (55) of the cis (H/Ph) but-2-ene (51) was also prepared to compare the activity of this less lipophilic compound with its parent.



The remaining three isomers (52, 53 and 54) would not crystallise as hydrochlorides, a result which may explain why the only compound previously isolated by the Lilly workers (Patent, 1953a) was Pyronil hydrochloride whose potent antihistaminic properties had earlier been reported by a group of pharmacologists from the same Company (Anderson et al. 1952). The residual base in the mother liquors was recovered, acidified with ethanolic hydrogen bromide, and the product fractionally crystallised to produce the three remaining isomers (52, 53 and 54) whose spectral characteristics are given in Table V. The major trans but-1-ene (54) hydrobromide, m.p. 191° , was initially isolated and continuation of the crystallisation over a period of several weeks eventually yielded crude samples of the last two isomers. Several recrystallisations in each case gave the cis but-1-ene (53) hydrobromide, m.p. $184-185^{\circ}$, and the trans (H/Ph) but-2-ene (52) hydrobromide, m.p. $152-153^{\circ}$. Thus, all four pure isomers (51, 52, 53 and 54) and the methiodide (55) were submitted for pharmacological testing.

(v) PHARMACOLOGICAL RESULTS AND DISCUSSION OF THE ANTI-HISTAMINIC ACTIVITIES OF FURTHER EXAMPLES OF 4-AMINO-1, 2-DIARYL BUTENE ISOMERS
N-Piperidino- and N-Pyrrolidino-1,2-diphenylbutene Isomers

The in vitro antihistaminic potencies of these isomers were assessed by their ability to antagonise histamine-induced

contractions of isolated guinea-pig ileum and the data obtained are given in Table VI. These results allow at best, semi-quantitative activity comparisons to be made as only when a highly active compound is uncovered are parallel dose-response curves determined from which a pa_2 value may be calculated. This constant pharmacological parameter for a compound can then be used for meaningful comparisons with other antihistamines.

However, it is clear that the two most active compounds (41 and 47) are both cis (H/Ph) but-2-enes which are effective at a concentration of 0.01 μ g/ml and cause over 95% inhibition three minutes after application and over 50% six minutes later. The cis (H/Ph)-4-piperidinobut-2-ene (41) is significantly more potent than its related isomers (43 and 44) while the 4-pyrrolidino isomers (47 and 50) although initially of similar activity, differ in duration of action, with the effect of the cis (H/Ph) but-2-ene (47) being more prolonged.

The cis (H/Ph)-4-piperidinobut-2-ene (41), is the most active member of the series and was found to have a pa_2 of 8.76 comparable to the value of 8.71 (Schild 1947) for the standard antihistamine, Mepyramine (37), which was used in these tests. This result precipitated examination of compound (41) in greater detail and its in vivo antihistaminic activity was assessed in the anaesthetized guinea-pig. Animals were prepared for recording the

TABLE VI

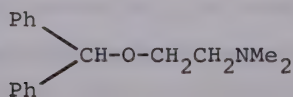
INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM BY
N-PIPERIDINO- AND N-PYRROLIDINO-1,2-DIPHENYLBUTENES

Sample	Compound Number in text	Conc. µg/ml	Percentage inhibition at time (in min.)											
			3	6	9	12	15	18	21	24	27			
4(1-piperidino)cis (H/Ph)but-2-ene.HCl	(41)	0.01	100	99	97	90	76	72	64	42	26			
4(1-piperidino)trans but-1-ene.HCl	(44)	0.10	88	75	51	37	21	-	-	-	-			
4(1-piperidino)cis but-1-ene.HCl	(43)	0.10	88	83	77	52	32	20	5	-	-			
4(1-pyrrolidino)cis (H/Ph)but-2-ene.HCl	(47)	0.01	96	74	52	37	26	14	10	-	-			
4(1-pyrrolidino)trans but-1-ene.HCl	(50)	0.01	100	60	37	22	5	-	-	-	-			
" .HBr	(50)	0.10	92	87	76	76	70	62	44	30	24			
Mepyramine standard	(37)	0.001	81	50	50	20	5	-	-	-	-			
4(1-piperidino)cis(H/Ph) but-2-ene methiodide	(46)	1.0	100	56	31	70	-	-	-	-	-			
Mepyramine standard	(37)	0.001	94	77	47	31	15	0	-	-	-			
"	"	"	100	95	73	57	0	-	-	-	-			

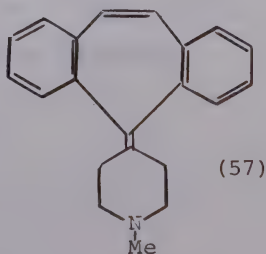
N.B. In this table, a dash denotes discontinuation of experimental observation.

resistance of the lungs to positive inflation following the method of Konzett and Rossler (1940). The intravenous injection of acetylcholine, histamine, 5-hydroxytryptamine or bradykinin normally causes a temporary increase in the resistance of the lungs to positive pressure inflation, and following the application of these spasmogens, compound (41) was found to selectively antagonise only the effect of histamine which clearly demonstrated its potent and specific antihistaminic activity in whole animals.

Depression of the CNS by the cis (H/Ph) piperidino-but-2-ene (41) were then considered as sedation is one of the most common side-effects of antihistaminic drugs in clinical use, and thus experiments were undertaken to determine whether compound (41) caused any such effect. Winter (1948) had reported that the ability of a drug to potentiate the duration of a drug-induced hypnosis can be used to assess its sedative activity and therefore the effects of compound (41) together with the commercial antihistamines chlorpheniramine (5), Mepyramine (37) Benadryl (56) and Cyproheptidine (57) on hexobarbitone-induced hypnosis in



(56)



(57)

the mouse were determined. The antihistamines were administered orally one hour prior to the intravenous injection of hexobarbitone (50 mg/kg) and the mice were observed at five minute intervals until all animals regained their righting reflex. The results are shown in Table VII and compound (41) just as Mepyramine, Benadryl and Cyproheptidine, significantly potentiated the hexobarbitone induced sleeping time in mice. This depression of the CNS precluded potential utilisation of compound (41) in any clinical trials but nevertheless the extreme activity and specificity of action of the cis (H/Ph) but-2-ene isomer was of great interest in our structure:activity studies.

An attempt to remove the undesirable CNS depressant properties of (41) with full retention of its antihistaminic activity by formation of the quaternary methiodide derivative (46) was unsuccessful, as seen by the pharmacological results in Table VI for this compound. Antihistaminic activity of this compound was only evident at a very high solution concentration of 1.0 µg/ml.

However, all these pharmacological results on the N-piperidino- and N-pyrrolidino-1,2-diphenyl butene isomers further emphasised the association of cis (H/Ph)1,2-diaryl-butenes with optimum antihistaminic activity.

TABLE VII

SEDATIVE ACTIVITIES OF COMMERCIAL ANTIHISTAMINES AND THE CIS (H/Ph) 4-PIPERIDINO

-1,2-DIPHENYLBUT-2-ENE IN THE MOUSE

Antihistamine	Number in text	Oral dose mg/kg	Mean sleeping time (min) \pm S.E. following hexobarbitone at 50 mg/kg I.V.
-	-	-	10.0 \pm 3.01
Chlorpheniramine	(5)	10	9.5 \pm 3.18
Mepyramine	(37)	10	19.5 \pm 2.71
Benadryl	(56)	10	29.0 \pm 4.35
Cyproheptidine	(57)	10	>50
cis (H/Ph) 4-piperidino -but-2-ene.HCl	(41)	10	30.0 \pm 2.61

1(p-Chlorophenyl)2-phenyl-4(1-pyrrolidino)butene or
'Pyronil' isomers

The comparative antihistaminic activities of the four Pyronil isomers (51, 52, 53 and 54) and the methiodide derivative (55) were assessed by the normal in vitro tests, using isolated guinea-pig ileum. The results obtained to date are shown in Table VIII and the trans (H/Ph) but-2-ene (52) is the most potent isomer of the three examples so far tested. It had a pA_2 value of 7.97 which indicated high activity and in addition, specific in vivo antihistaminic action was again demonstrated in anaesthetized guinea-pigs by the method previously described (see page 53)

The quaternary methiodide (55) had low activity but the but-1-ene isomers (53 and 54) were quite active and the more potent trans compound (54) had a fairly prolonged duration of effect, exhibiting over 50% inhibition after 15 minutes. The pA_2 value for the latter compound was determined as 7.4 which confirmed its reduced activity compared to the trans (H/Ph) but-2-ene (52) isomer (pA_2 7.97).

Determination of the pA_2 value of a commercial sample of Pyronil phosphate, which has the cis (H/Ph) but-2-ene (51) structure (see page 51), is now in progress for comparative purposes (the insolubility of the corresponding hydrochloride precluded its pharmacological evaluation). It is anticipated that Pyronil will prove to be

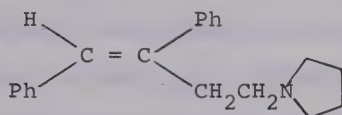
TABLE VIII

INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM BY THE
1 (p-CHLOROPHENYL) 2-PHENYL-4 (1-PYRROLIDINO) BUTENE ISOMERS

Sample	Compound Number in text	Conc. μg/ml	Percentage inhibition at time (in min.)											
			3	6	9	12	15	18	21	24	27	30	33	
<u>trans</u> (H/Ph)but-2-ene.HBr	(52)	0.10	82	75	46	57	45	38	-	-	-	-	-	
"	"	"	100	100	100	100	100	100	100	76	64	40	40	
"	"	0.001	24	19	14	9	0	-	-	-	-	-	-	
Mepyramine standard	(37)	0.001	49	36	27	19	15	-	-	-	-	-	-	
"	"	"	50	31	28	6	0	-	-	-	-	-	-	
"	"	"	62	46	24	13	0	-	-	-	-	-	-	
<u>trans</u> but-1-ene.HBr	(54)	0.01	69	65	62	53	56	25	16	37	13	0	-	
<u>cis</u> but-1-ene.HBr	(53)	0.01	45	41	28	17	0	-	-	-	-	-	-	
No comparative figures for the standard (Mepyramine) were given with the above figures, but the pA ₂ value for compound (54) was determined as 7.4														
<u>cis</u> (H/Ph)but-2-ene methiodide	(55)	1.0	100	94	65	41	29	12	0	-	-	-	-	
"	"	0.01	63	31	13	0	-	-	-	-	-	-	-	
Mepyramine standard	(37)	0.001	94	77	47	31	15	0	-	-	-	-	-	
"	"	"	100	95	73	57	0	-	-	-	-	-	-	

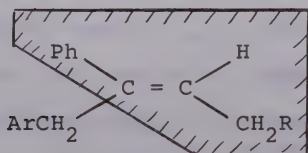
N.B. In the table, a dash denotes discontinuation of experimental observation.

the most active of the four isomers in line with previous data on other sets of compounds. However, the moderate potencies of the trans (H/Ph) but-2-ene and both but-1-enes of the Pyronil group together with the fairly high activity shown by another N-pyrrolidino but-1-ene isomer (50) previously discussed (see p. 53), indicates a

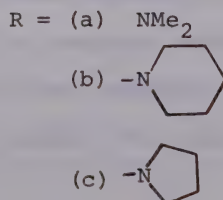


(50)

diminished stereospecific dependence for activity amongst N-pyrrolidino aminobutenes. This may possibly be due to their common basic group which might enhance interaction of these isomers with the receptors to a significant extent inspite of their unfavourable molecular geometries. This postulate is examined further at a later point (see p. 111) but generally speaking, all the pharmacological data presently available, suggests that the disposition of pharmacophoric groups in cis (H/Ph) but-2-enes (58) are optimal for antihistaminic activity, as shown by the high

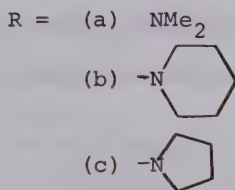
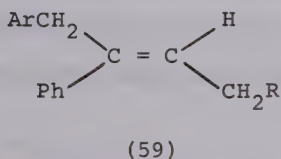


(58)



potency of these compounds and of the significant activity fall following a configurational change. This concept is in accord with previous studies (Casy and Pocha 1967; Casy and Parulkar 1969).

In cis (H/Ph) but-2-enes (58) the phenyl ring and the carbon-carbon double bond are coplanar (PMR and UV evidence) and also in the same molecular plane as the methyleneamino moiety (see shaded area of formular 58). This is in contrast to the trans (H/Ph) analogues (59), of lower antihistaminic potencies, in which the phenyl and olefinic bond planes greatly diverge as a result of non-bonded interactions between the phenyl ring and the adjacent methyleneamino group (UV and evidence of models).

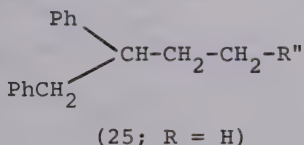


Assuming that the aromatic function(s) and the basic group are essential pharmacodynamic groups for antihistaminic activity in these aminoalkenes, then the planar area of cis (H/Ph) but-2-enes depicted in structure (58) may be of importance for maximum interaction and formation of the complex with the receptors. It therefore seemed of interest to disturb the planarity in

cis (H/Ph) but-2-ene examples by suitable structural changes and to ascertain the effect on antihistaminic activity.

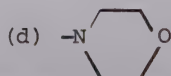
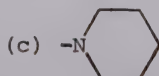
(vi) DISTURBANCE OF THE COPLANARITY BETWEEN THE PHENYL RING AND THE CARBON-CARBON DOUBLE BOND OF CIS (H/Ph) BUT-2-ENES (56)

One obvious structural change to distort the planarity in a cis (H/Ph) but-2-ene system was to reduce a suitable compound to the corresponding aminobutane. The latter saturated molecule is sterically crowded and the phenyl ring and the basic group cannot lie in the same molecular plane (evidence of models). Frey and coworkers (1950) had already prepared and examined a series of such aminobutanes (25; R = H) and their antihistaminic activities were much less than those of the precursor amino-



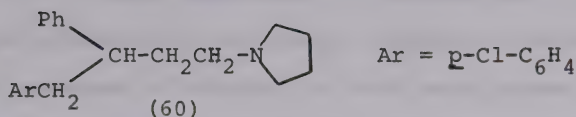
R'' = (a) NMe₂

(b) NEt₂



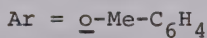
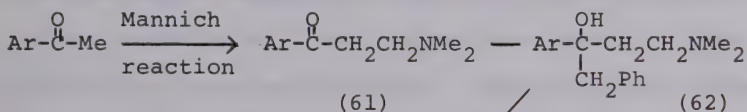
butenes. These data suggest that the lack of planarity amongst aminobutanes is responsible for reduced activity.

As part of our own study, a sample of the cis (H/Ph) but-2-ene (51) hydrochloride (Pyronil hydrochloride) was

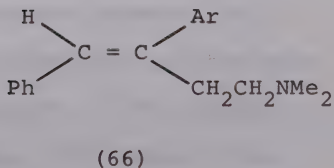
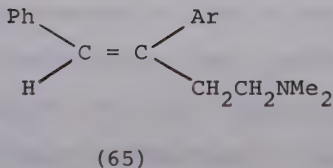
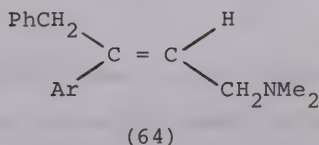
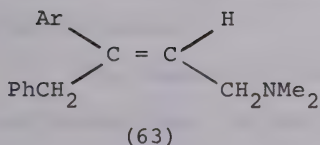


catalytically reduced to the corresponding aminobutane (60); it was found that the activity of this derivative was extremely low (for full pharmacological details, see Table IX).

The second approach was to prepare the o-tolyl carbinol (62) by the normal synthetic route and to dehydrate it to form the four aminobutene isomers (63, 64,



(-H₂O)



65 and 66). These compounds all contain the o-tolyl aromatic group which sterically interacts with adjacent groups (evidence of models) so that each isomer is distinctly non-planar in character. Acid-catalysed elimination of the tertiary alcohol (62) using a 2.5 hour reflux period (which allowed for isomeric equilibration) produced both but-1-enes (65 and 66) but only a single but-2-ene as shown by the vinylic region of the PMR spectrum of the total basic product (two singlets and a triplet visible). Acidification with ethanolic hydrogen chloride and a subsequent fractional crystallisation lead to the isolation of isomerically pure hydrochlorides of each of the three aminobutenes. Their spectral parameters are given in Table IX and assignment of configuration to the but-1-enes (65 and 66) was by the previously described method involving consideration of the overall planarity of each isomer.

The absence of the second but-2-ene in the elimination product was initially thought to be the result of an unusual kinetic effect by the o-tolyl group on the elimination mechanism rate of the aminobutene isomers; as it was desirable to have the PMR characteristics of the missing but-2-ene for comparative purposes, it was decided to repeat dehydration of the carbinol (62) using three different reaction periods to see whether the second but-2-ene might be present in the aminoalkenic product after

TABLE IX

SPECTRAL CHARACTERISTICS OF 4-DIMETHYLAMINO-1-PHENYL-2 (O-TOLYL) BUTENE ISOMERS

Sample	Compound Number(s) in text	Chemical shifts ^a			λ_{\max} (ϵ) ^d
		C-1 vinyl ^b	C-3 vinyl ^c	Others	
<u>cis</u> (H/Ar)but-2-ene.HCl	(63)	-	341.5	NCH ₂ CH: 235 ^e (J7) CH ₂ Ar 227 ^f NMe ₂ 166.5 ^b ArMe 127.5 ^b	end absorption
<u>cis</u> but-1-ene.HCl	(65)	396	-	NCH ₂ CH ₂ 182 ^g NMe ₂ 158 ^b ArMe 143 ^b	248 (14940)
<u>trans</u> but-1-ene.HCl	(66)	400.5	-	NCH ₂ CH ₂ 185 ^f NMe ₂ 168 ^b ArMe 126.5 ^b	255 (15240)
Total base elimination product	(63) (64) (65) (66)	387 381.5	329.5	ArMe 132 " 137.5 " 140	-

^a Chemical shifts in Hz from TMS (internal standard)

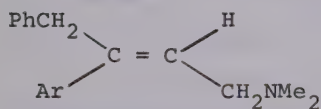
at an operating frequency of 60 MHz; solvent

CDCl₃, coupling constants (J) in Hz.^b Singlet.^c Triplet (J7).^d Solvent water; λ_{\max} is wavelength in m μ ; extinction coefficient (e) shown in parenthesis.^e Doublet.^f Broad singlet.^g Centre of broad multiplet.

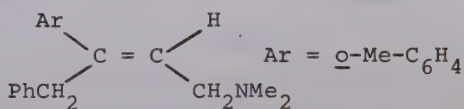
either a short or very long equilibration period. In fact, only the same but-2-ene isomer that had already been isolated appeared in the PMR spectrum of the reaction product after either 0.25, 1.0 or 85 hours. The ratios of the three isomers present (calculated from amplified integrals of the vinylic signals) varied very little as shown below but the complete absence of the

<u>Reflux Period (Hr.)</u>	<u>% Trans-1-ene</u>	<u>Cis-1-ene</u>	<u>But-2-ene</u>
0.25	27	39	34
1.0	24	37	39
85	20	30	40

second but-2-ene isomer indicated a highly unfavoured structure from a thermodynamic viewpoint. Examination of molecular models (Catalin and Framework) strongly suggested that the energetically unfavoured compound was the trans (H/Ar) isomer (64). In this molecule, severe non-bonded interactions occur between the o-tolyl methylene-amino groups in juxtaposition. However, steric interaction



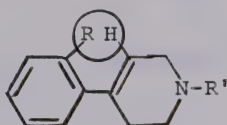
(64)



(63)

between the o-tolyl and vinylic hydrogen of the cis (H/Ar) but-2-ene (63) was also undoubtedly in operation so that in both the cis and trans but-2-ene isomers there was no

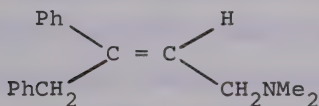
possibility of a UV styrenoid chromophore which precluded the use of this spectroscopic method for a configurational assignment. The steric clashing of vinylic and o-tolyl groups cis to one another has been reported previously following a UV study on a series of tetrahydropyridines (67) which exhibited end absorption or greatly reduced absorption maxima whenever the ortho



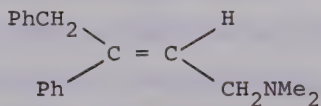
(67)

group (R) was other than hydrogen (Fullerton 1960).

However, the configuration of the o-tolyl but-2-ene isolated has been deduced by comparison of its PMR



(33)



(32)

parameters with those of the cis and trans (H/Ph)1,2-diphenyl analogues (32 and 33). The appropriate PMR characteristics of the three compounds are shown below and the methyleneamino (231 Hz) and the dimethylamino (166 Hz) chemical shift positions of the cis (H/Ph) diphenyl but-2-ene (33) agree very closely with the

respective figures of 235 and 166.5 Hz for the o-tolyl isomer, but there are significant shift differences between the vinylic and benzylic proton signals of these two isomers. The absorption frequencies of the latter two groups are markedly higher field in the o-tolyl but-2-ene. These variations in chemical shifts together with

<u>Compound</u>	Chemical Shifts (Hz) relative to TMS in CDCl ₃ solution			
	<u>Vinylic</u>	<u>CH₂Ph</u>	<u>NCH₂CH: NMe₂</u>	
<u>o</u> -tolylbut-2-ene <u>hydrochloride</u>	341.5	227	235	166.5
<u>cis</u> (H/Ph) diphenyl but-2-ene (33) <u>hydrobromide</u>	378	240	231	166
<u>trans</u> (H/Ph) diphenyl but-2-ene (32) <u>hydrochloride</u>	358	225	213.5	160

the comparable values in the o-tolyl and cis (H/Ar) diphenyl but-2-ene isomers have been interpreted as indicative of the former's configuration as the o-tolyl cis (H/Ar) but-2-ene (63) by the following arguments:

The probable spatial arrangement of the cis but-2-ene o-tolyl isomer is depicted in Figure 2 with the o-tolyl ring existing in a preferred conformation which involves twisting of the aromatic function out of the plane of the double bond. The o-tolyl group in this conformation exerts a screening effect on both the vinylic

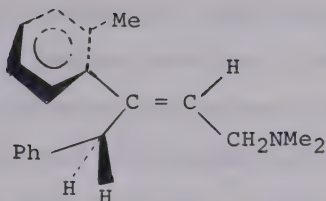


Figure 2. Probable preferred conformation of the cis H/o-tolyl)but-2-ene (63).

and benzylic protons which lie in the shielding cone of the aromatic ring. Thus the chemical shifts of these two proton groups should fall at significantly higher field in the o-tolyl but-2-ene (63) than in the corresponding diphenyl isomer (33) whose 2-phenyl function is coplanar with the olefinic bond and hence deshielding in effect on other groups in the molecule.

Moreover, in the o-tolyl structure (63) the remote dimethylaminomethyl grouping should be largely unaffected by the non-planar orientation of the o-tolyl ring, as Tobey (1969) has demonstrated that aryl groups have negligible effects on the shifts of groups trans to them. In addition, any anisotropic effect exerted by the cis benzylic aromatic function in the o-tolyl compound should be very close to that operating in the cis (H/Ph) diphenyl isomer (33) as these groups will have very similar conformational tendencies.

Finally, it should be noted that in all previous eliminations of 1,2-diarylcarbinols (see earlier) the trans (H/Ph) but-2-enes have always proved to be the minor isomer (in such low abundance as 5%) in the four component aminoalkene mixtures. As the trans (H/Ar) but-2-ene (64) in the o-tolyl case is sterically unfavoured even more than usual it is not too surprising that no trace of this isomer was evident in the PMR spectrum of the elimination reaction product.

(vii) PHARMACOLOGICAL RESULTS AND DISCUSSION OF COMPOUNDS DESCRIBED IN (vi)

The pharmacological data obtained are shown in Table X. The reduced Pyronil structure (60) shows markedly decreased activity compared to its aminobutene parents (see Table VIII).

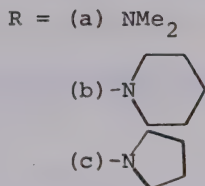
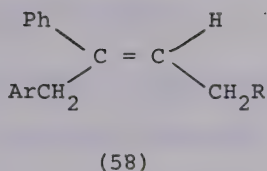
In the case of the o-tolyl isomers, the but-1-enes (65 and 66) are significantly less potent than the cis (H/Ar) but-2-ene (63), which causes 92% inhibition after three minutes at the low dose level of 0.01 µg/ml. This initial potent effect decreases rapidly with time and is completely absent after 12 minutes. It is significant that the potency of the cis (H/Ph) but-2-ene (63) isomer is undoubtedly less than that of the corresponding diphenyl cis (H/Ph) but-2-ene (33) (see Table IV). Moreover, the decreased activity shown by the four compounds in which the

TABLE X

INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM
BY NON-PLANAR ANTIHISTAMINIC STRUCTURES

Sample	Compound Number in text	Conc. in $\mu\text{g/ml}$	Percentage inhibition at time (in min.)					
			3	6	9	12	15	18
'Reduced Pyronil'	(60)	1.0	85	37	0	-	-	-
Mepyramine standard	(37)	0.001	94	77	47	31	15	0
"	"	"	100	95	73	57	0	-
"	"	"	50	29	18	-	-	-
"	"	"	69	52	38	10	0	-
<u>o-Tolyl Derivatives</u>								
<u>cis</u> (H/Ar) but-2-ene.HCl	(63)	0.01	92	38	12	0	-	-
<u>cis</u> (H/Ar) but-1-ene.HCl	(65)	0.01	20	-	-	-	-	-
Mepyramine standard	(37)	0.001	81	50	20	5	-	-
<u>trans</u> but-1-ene.HCl	(66)	0.10	32	23	-	-	-	-
Mepyramine standard	(37)	0.001	49	36	27	25	19	15
"	"	"	50	31	28	3	6	0
"	"	"	62	46	24	19	13	0

N.B. In this table, a dash denotes discontinuation of experimental observation.



overall planarity is disturbed lends further support to the postulate that the molecular geometry of cis (H/Ph) but-2-enes (58) is optimal as a result of the Ar ring, olefinic bond and methyleneamino group all lying close to a mean molecular plane.

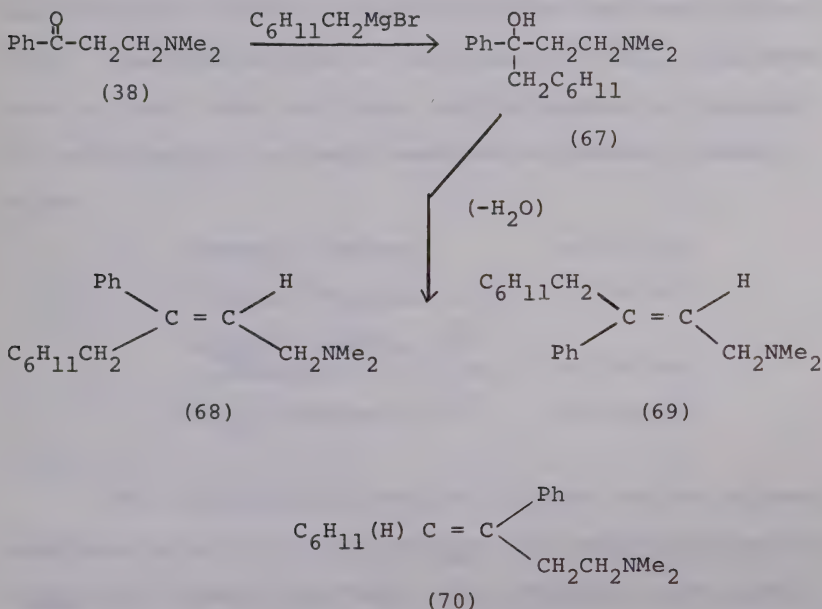
(viii) THE ROLE OF THE AROMATIC GROUPS IN cis (H/Ph)1,2-DIARYLBUTENES

The structure:activity relationships so far discussed and the previous studies of Casy and his group (1967 and 1969) indicate that cis (H/Ph) but-2-enes (58) possess optimal molecular arrangements for antihistaminic activity. It has been proposed (see page 60) that the planar region present in such compounds is an important general feature for antihistaminic potency, but as yet the exact role of the aromatic groups present in cis (H/Ph) but-2-enes and other aminobutene isomers is unclear. It was thus considered of interest to study the biological activities of new structures in which the aromatic rings were replaced by groups which had widely differing steric and electronic

characteristics such as the cyclohexyl, 2-pyridyl and t-butyl (t-Bu) moieties.

(a) Replacement of the Benzyl Ring by the Cyclohexyl and 2-Pyridyl Moieties

The role of the benzyl ring as an adjunct for antihistaminic activity amongst aminoalkenes was initially studied and the cyclohexyl carbinol (67) was synthesized



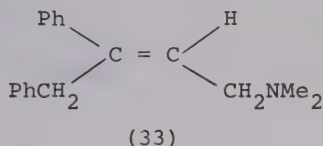
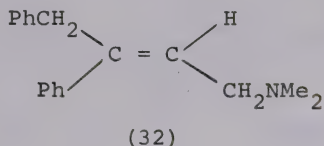
as the necessary intermediate for preparation of aminoalkene isomers containing a cyclohexylmethyl grouping. The tertiary alcohol (67) was prepared by a Grignard

reaction in poor yield (17%) and its dehydration in the normal manner yielded a mixture of both but-2-enes (68 and 69) together with only a very minor amount (5%) of a but-1-ene (70) (but-1-enes are clearly unfavoured when an extended stilbene feature cannot arise). Fractional crystallisation of the hydrochloride mixture produced several crystal crops whose m.p. ($243-244^{\circ}$) agreed exactly with the cyclohexyl aminobutene obtained by Frey and coworkers (1950) who had eliminated the same carbinol (67). The PMR spectrum of the product in CDCl_3 indicated that it was a pure but-2-ene (no duplication of signals); it exhibited the following assignable resonance absorptions:

Phenyl (singlet)	at 440 Hz
Vinylic (triplet; J 7.5)	at 355 Hz
NCH_2CH : (doublet of doublets; J 7.5 and 5)	at 230 Hz
NMe_2 (doublet; J 5)	at 168 Hz

The corresponding vinylic triplets for the diphenyl analogues were at 378 for the cis (33) and 358 Hz for the trans (32) isomer (see Table III), which at first sight favoured a trans structural assignment to the cyclohexyl compound. However, these vinylic shift values may be misleading if used for the assignment of configuration to the cyclohexyl isomer as steric interactions of the $\text{C}_6\text{H}_{11}\text{CH}_2$

group (this moiety is bulkier than PhCH_2) probably lead to a different conformationalequilibrium than obtains in either of the benzyl analogues (32 and 33).

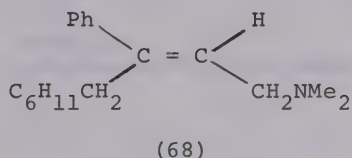


Indeed, comparison of the NCH_2CH : and NMe_2 resonance absorptions of the three compounds which agreed very

<u>Compound</u>	Chemical shifts (Hz) relative to TMS in CDCl_3 solution	
	<u>NCH_2CH:</u>	<u>NMe_2</u>
1-cyclohexyl-2-phenyl-4-dimethylaminobut-2-ene <u>hydrochloride</u> (68) or (69) (of unknown configuration)	230	168
<u>cis</u> (H/Ph) diphenyl but-2-ene (33) <u>hydrobromide</u>	231	166
<u>trans</u> (H/Ph) diphenyl but-2-ene (32) <u>hydrochloride</u>	213.5	160

closely (see above) suggested that the configuration of the cyclohexyl but-2-ene was the cis (H/Ph) but-2-ene (68). This supposition was confirmed by the UV spectrum of the hydrochloride (68) in water, which exhibited an absorption maximum (λ_{max} 238 m μ , ϵ 11850) characteristic of a styrenoid chromophore, which was attributed to the cis

(H/Ph) but-2-ene (68) the only but-2-ene isomer which has its phenyl ring and double bond in the same molecular plane (see p. 37).

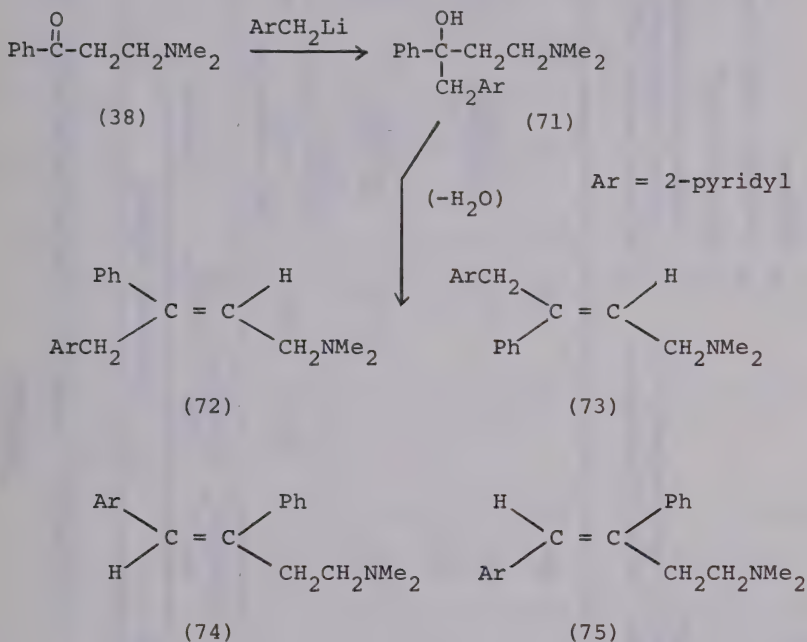


It therefore appeared that the vinylic chemical shift exhibited by compound (68) was anomalously high field and this may be due to the $\text{NCH}_2\text{CH:}$ /vinylic spatial relationship being more disturbed by the $\text{C}_6\text{H}_{11}\text{CH}_2$ substituent in (68) than by the corresponding PhCH_2 function in the analogue (33). Dreiding models indicate that the geminal $\text{Ph/CH}_2\text{R}$ interaction in these compounds is more serious than $\text{R} = \text{C}_6\text{H}_{11}$ than when $\text{R} = \text{Ph}$; this deflects the $\text{C}_6\text{H}_{11}\text{CH}_2$ group away from the Ph ring and towards the CH_2NMe_2 function in structure (68) which causes serious steric clashing between the latter two groups.

Hence the solitary cyclohexylaminobutene isomer obtained from dehydration of the alcohol (67) was fortunately the most useful compound for continuation of the structure:activity studies.

The carbinol (71), which contained the 2-pyridyl nucleus as the benzyl aromatic function, was then prepared by the method of Casy and Pocha (1967). These authors had

reported the appearance of all four possible aminobutenes (72, 73, 74 and 75) after base catalysed elimination of this tertiary alcohol and a subsequent fractional crystallisation of the acidified product had yielded a sample of



the trans but-1-ene (75) dihydrochloride. Elimination of the carbinol (71) using an acetic-hydrochloric acid mixture had failed and therefore more vigorous acid conditions were used in our own study. The carbinol (71) was treated with 85% aqueous sulphuric acid solution at 100-110° for 2.5 hours and the PMR spectrum of the basified product showed the presence of both but-1-enes (74

TABLE XI

SPECTRAL CHARACTERISTICS OF 1-(2-PYRIDYL) 2-PHENYL-4-DIMETHYLAMINO-BUT-1- AND BUT-2-ENES

Sample	Compound number in text	Chemical shifts ^a				λ_{\max} (ϵ) ^e
		C-1 vinyl ^b	C-3 vinyl ^c	NMe ₂ ^b	Others	
trans but-2-ene dihydrogen oxalate	(73)	-	357.5	165	CH ₂ -2-pyridyl 256d NCH ₂ CH: 222h (J7.5)	end absorption
cis but-1-ene dihydrogen oxalate	(74)	414	-	173.5	CH ₂ CH ₂ N 193d	246 (6350) 294 (6000)
base from above salt ^f	(74)	402	-	-	-	-
trans but-1-ene.2HCl ^g	(75)	422	-	173	CH ₂ CH ₂ N 198d	260.5 (11980) 293 (14500)
base from above salt ^{f,g}	(75)	406	-	139	-	-

^a Chemical shifts in Hz from DSS (internal standard) at an operating frequency of 60 MHz; solvent D₂O, coupling constants (J) in Hz.

^b Singlet.

^c Triplet (J7.5)

^d Broad singlet.

^e Solvent water; λ_{\max} is wavelength in m μ ; extinction coefficient (ϵ) shown in parenthesis.

^f Solvent CDCl₃.

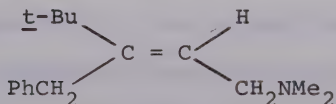
^g Casy and Pocha (1967).

^h Doublet.

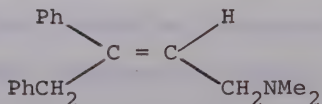
and 75) together with a single but-2-ene (see Table XI), as shown by the appearance of two singlets and a triplet in the vinylic region of the spectrum. The total base product was acidified with ethanolic hydrogen chloride but no dihydrochloride compounds could be induced to crystallise. Solid oxalates of the basic mixture were obtained, however, and numerous recrystallisations of these led to the isolation of pure samples of the cis but-1-ene (74) and the trans but-2-ene (73) dihydrogen oxalate salts. The diagnostic spectral parameters of these isomers are shown in Table XI together with the isomer (75) isolated by Casy and Pocha (1967).

(b) Replacement of the 2-Aryl Ring by the t-Butyl Group and Related Studies

It was decided to synthesise and attempt to isolate the t-Bu analogue (76) of a typical cis (H/Ph) but-2-ene (33) to examine the effect of replacing the 2-phenyl group by a bulky non-aromatic function. A comparative pharmacological evaluation of the two compounds (33 and 76) was



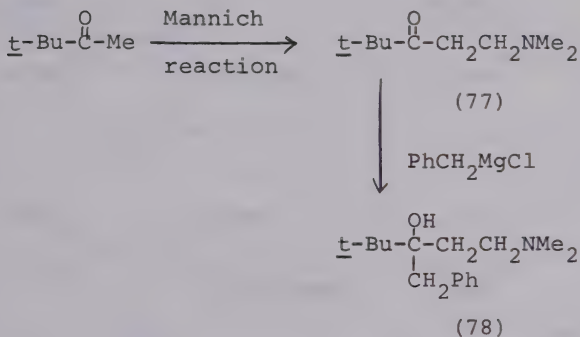
(76)



(33)

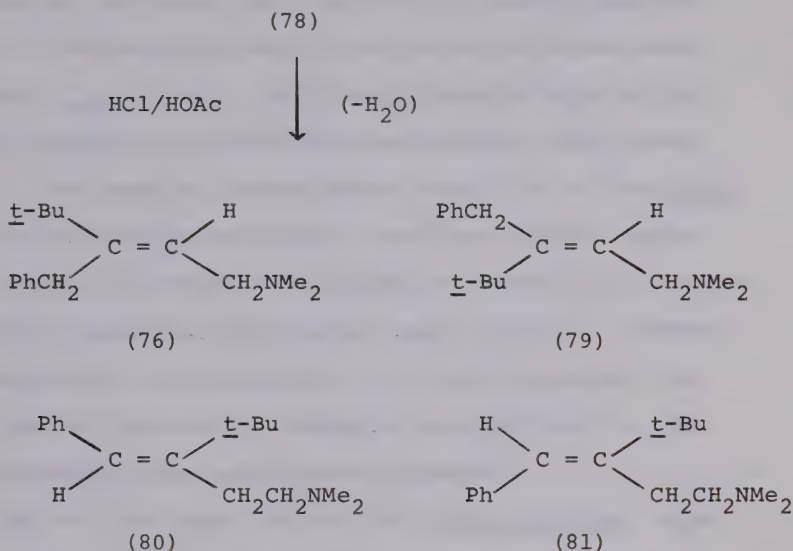
then envisaged to evaluate the importance of the 2-aryl ring in cis (H/Ph) but-2-enes for effective interaction and blockade of the histamine receptors.

The preparative scheme involved formation of the Mannich base (77) using pinacolone as the reaction substrate, followed by addition of benzylmagnesium chloride to the aminoketone to produce the desired tertiary alcohol (78).



Acid-catalysed elimination of the carbinol followed by the usual work-up yielded an aminoalkenic mixture. The PMR spectrum showed that only three of the four possible butenes (76, 79, 80 and 81) had been formed as indicated by the presence of three distinct NMe₂ singlets and three vinylic signals (two triplets characteristic of 79 and 80; one singlet characteristic of either 81 or 82) in the appropriate resonance regions. There was no breakdown of the t-Bu signals which indicated the absence of any

Wagner-Meerwein products. These might theoretically occur by rearrangement of the t-Bu group via the carbonium ion intermediate in the E-1 elimination reaction.



The individual components were separated as hydrochloride salts after fractional crystallisation over several weeks and the various configurational assignments based on PMR (see Table XII) and UV spectroscopic evidence are described below:

(1) The trans (t-Bu/Ph) but-1-ene (81) hydrochloride, m.p. 176-177°. Catalin models indicated that non-bonded interactions between the various double-bond substituents in this compound were of a less serious order than in the cis

but-1-ene (80) isomer which had its t-Bu and phenyl functions cis to one another. The sole but-1-ene formed was thus assigned a trans configuration since this isomer was undoubtedly the more stable form, the elimination procedure being one which allowed equilibration. UV evidence was corroborative as the absorption maximum (λ_{max} 238 m μ , ϵ 8600) was characteristic of, at least, a partially effective phenyl-double bond chromophore. The superior thermodynamic stability of the trans compared to the cis but-1-ene isomer was further emphasised by equilibration of the pure but-1-ene (81) in a hot acetic-hydrochloric acid mixture which failed to produce the second but-1-ene compound (no vinylic signals other than that of the starting material were evident in the PMR spectrum of the equilibrated product).

(2) The two but-2-ene (76 and 79) hydrochlorides, m.ps. 243° and 183-184°. Integrals of the two vinylic PMR signals in the total elimination mixtures indicated that the former preponderated slightly. The PMR spectra of the pure hydrochloride isomers (see Table XII) differed in several respects, most notably in regard to the t-Bu signal; the lower m.p. (183-184°) hydrochloride exhibited two signals which could only be attributed to the presence of a magnetically non-equivalent t-Bu group. A sharp six plus a broad three proton singlet (w_{H} 2.5 Hz) were evident in the high-field region of the spectrum (see Figure 3 for

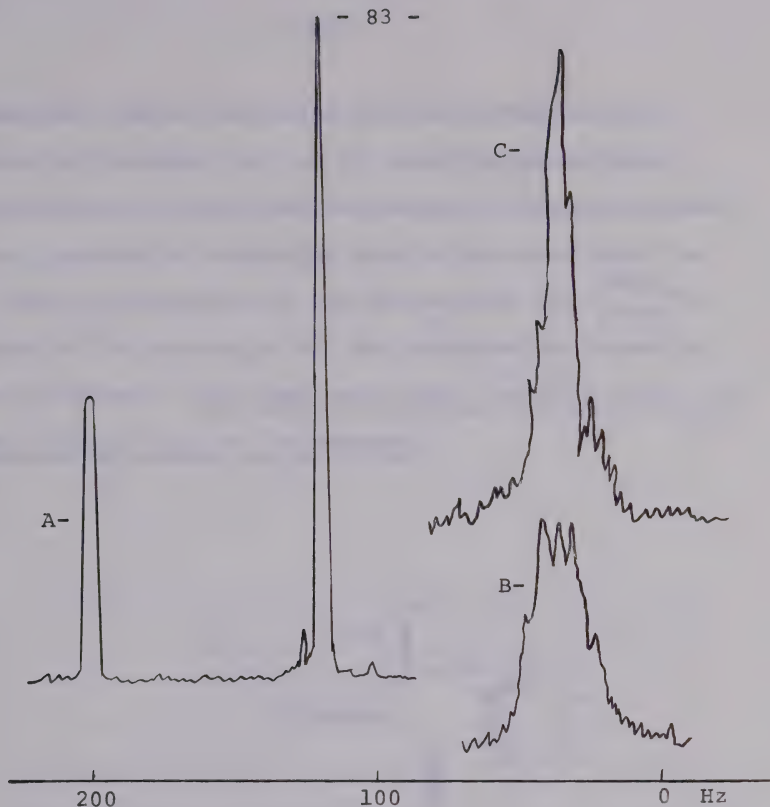


Figure 3. 100 MHz Signals arising from the magnetically non-equivalent t-Bu group contained in the t-Bu aminobut-2-ene, m.p. $183-184^{\circ}$ in DMSO-d_6 . A: both signals at room temperature. B: 3-proton (lower field) signal at 100° . C: 3-proton signal at 100° when sample irradiated at the frequency of the vinylic signal (sweep width 1000 Hz for A, 100 Hz for B and C).

the 100 MHz spectrum). The latter, originally noted in the spectra of mixtures from the progressing fractional crystallisation, was first thought to be an impurity but its persistence in the spectrum of an analytical sample showed it

to represent one of the three t-Bu/Me proton groups. A unique environment for one of these Me groups must be responsible for the observed magnetic non-equivalence, and manipulation of molecular models indicated that the most likely explanation is the adoption by the $\begin{array}{c} \text{PhCH}_2 \\ \text{t-Bu} \end{array} \text{C} =$ fragment of the molecule, of the preferred conformation shown in Figure 4, provided restricted rotation about the t-butyl-alkene link may be assumed.

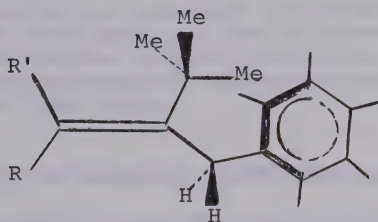


Figure 4. The postulated preferred conformation of the 2-t-Bu-4-dimethylemaino-1-phenyl-but-2-ene isomer exhibiting magnetic non-equivalence of its t-Bu group.

In this conformation two of the t-Bu Me groups are in essentially equivalent environments (allowing for some degree of rotational freedom about the -CH₂-phenyl linkage) while the third group lies in the plane of the double bond. This latter Me group falls in the deshielding cone of the

anisotropic carbon-carbon double bond (ApSimon et al. 1967) which accounts for its lower field position compared to the other two Me groups. The alternative coplanar conformation (see Figure 5) cannot feasibly

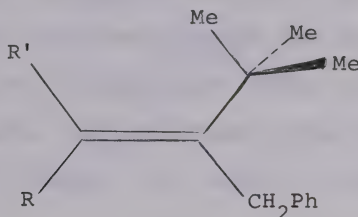


Figure 5. Alternative coplanar conformation of the t-Bu group in the 2- t-Bu -4-dimethylamino-1-phenylbut-2-ene isomer showing magnetic non-equivalence of its t-Bu group.

explain the observed t-Bu chemical shifts because this arrangement requires the solitary Me group to be shielded and hence higher field than the remaining two Me functions. No other conformations of the molecule seemed likely to produce the necessary restricted rotation of the t-Bu group and although the magnetic influence of the benzylic aromatic ring in the postulated preferred conformations (see Figure 4) was difficult to assess from models it did appear more likely to augment the deshielding effect of the olefinic bond.

As the conformation depicted in Figure 4 qualitatively explains the observed t-Bu signals it should now be considered how this arrangement might arise; the aromatic ring

must be deflected towards the t-Bu substituent as a result of steric clashing with the adjacent R substituent. This grouping is either the vinylic hydrogen or the large dimethylaminomethyl radical and only the latter bulky group can be expected to instigate reorientation of the benzyl function. This provides evidence for the configuration of the but-2-ene hydrochloride isomer (m.p. 183-184^o) possessing a magnetically non-equivalent t-Bu group as being the cis (t-Bu/H) isomer (76), with R = CH₂NMe₂ and R' = H in Figure 4.

In the trans isomer (79) a partial conformation as in Figure 6 is more probable as the t-Bu group is cis to the bulky methyleneamino moiety so that, in this case, the aromatic ring is free to move towards the vinylic substituent. This allows free rotation of the t-Bu function so that each Me is equivalent and the group comes to resonance as a sharp nine proton singlet.

Double resonance experiments at 100 MHz on the cis (t-Bu/H) but-2-ene (76) reveal that the vinylic (and benzylic) protons are weakly spin-spin coupled ($J = 0.6$ Hz) to the isolated three proton t-Bu methyl signal (see Figure 3) (the six-proton signal remained a sharp singlet at higher field). This observation further supports a coplanar Me-double bond conformation which allows the coupled protons separated by greater than three bonds to

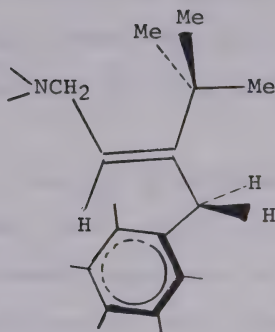


Figure 6. The proposed partial conformation of the trans (t-Bu/H)-aminobut-2-ene (79) isomer.

be linked by near-planar zig-zag paths (showed in Figure 7 for Me and vinyl protons). Such a closely coplanar 'W' configuration is an established requirement for long-range spin-spin coupling (Sternhell 1964; 1969; Garbisch 1964).

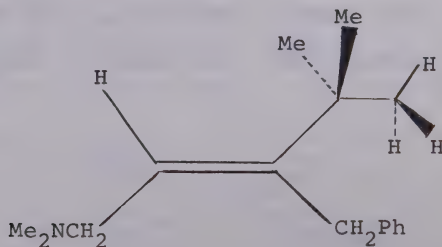
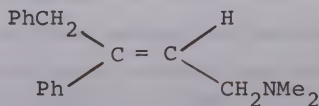


Figure 7. The coplanar 'W' configuration of the isolated Me group and the coupled vinylic (and benzylic) protons in the cis (t-Bu/H)but-2-ene (76) isomer.

The remainder of the PMR spectral differences between the but-2-ene isomers can now be interpreted in terms of the conformations depicted in Figures 4 and 6 as follows:

Vinylic signals. In the cis (t-Bu/H) but-2-ene (Figure 4; $R' = H$; $R = CH_2NMe_2$) the vinylic proton is remote from the benzylic aromatic group but in the trans isomer (Figure 6) these functions are much closer in space; hence the aromatic influence upon the vinylic resonance should be greater in the trans (t-Bu/H) compound, and in fact the trans signal (352 Hz) is significantly lower field than that of the corresponding cis proton (315 Hz). This fact is in accord with the anticipated deshielding effect of the aromatic ring in the partial conformation shown in Figure 6. In addition, the trans value (352 Hz) corresponds closely with the vinylic chemical shift (358 Hz) observed for the 1,2-diphenyl butene (32) (see Table III) whose vinylic hydrogen has a very similar molecular environment.



(32)

Benzyl methylene signals. From the modified Shoolery rules (Dailey and Shoolery 1955; Royal Institute of Chemistry Summer School 1964) the expected chemical shift for $\text{Ph}\underline{\text{CH}}_2$ in a $\text{PhCH}_2\text{C}(\underline{\text{t}}\text{-Bu}) = \text{CHCH}_2\text{NMe}_2$ structure is 198 Hz at 60 MHz*; thus the cis signal (161.5 Hz) has an unusually high field, and the trans (215 Hz) a low field position. Diagrams for the theoretical shielding zones (ApSimon et al. 1967) arising from a carbon-carbon double bond predict that the methylene protons of the cis isomer (76) will be screened and high field in the preferred conformation shown in Figure 4 ($\text{R}' = \text{H}$; $\text{R} = \text{CH}_2\text{NMe}_2$). Conversely, the methylene protons of the trans isomer (79) depicted in Figure 6 will be at lower field than the expected value as a result of their presence in the deshielding cone of the double bond. Thus, the deviation from the calculated chemical shift values are consistent with the assigned configurations.

Methyleneamino and dimethylamino signals. The similar resonance positions of the isomeric $\underline{\text{CH}}_2\text{N}$ and NMe_2 signals show that the cis and trans dimethylaminomethyl substituents differ little in their molecular environments. This

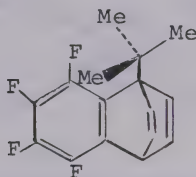
* $\tau_{\text{CH}_2} = 8.75 - \Sigma 0.75 (\text{C}=\text{C}) + 1.3 (\text{Ph}) = 6.7$ (198 Hz) (the methylene protons are flanked by the double bond and phenyl groups in the structure)

is only likely to be the case if the aromatic group is removed from the aminomethyl function in the cis (t-Bu/H) isomer (76) (as it must be in the trans form). An arrangement of this type is an essential feature of the proposed cis conformation (Figure 4, $R' = H$; $R = CH_2NMe_2$) which therefore receives further support.

At this point, it was decided to investigate further the observed magnetically non-equivalent t-Bu group and PMR temperature studies in $DMSO-d_6$ at 100 MHz were carried out. It was anticipated that at higher temperatures the remote Me group in the cis (t-Bu/H) but-2-ene (76) might be freely rotating or less restricted to cause the separate t-Bu signals to coalesce into a solitary singlet or move more closely together. However, the separation of the t-Bu singlets diminished only slightly as the temperature was raised (separations: 80.4 Hz at room temperature, 75.6 Hz at 100° , 72.4 Hz at 150° and 71.8 Hz at 180°). This indicated that observation of the non-equivalent signal must be associated with large barriers to rotation of the t-Bu group about its link to the double bond, as may reasonably be expected on account of the highly crowded nature of the cis molecule (see Figure 4, $R' = H$; $R = CH_2NMe_2$).

The question of the novelty or otherwise of the phenomenon of a magnetically non-equivalent t-Bu group then arose and, accordingly, a thorough literature search

was made. Although four low temperature examples were noted, only a single previous report of non-equivalence within a t-Bu group at normal temperatures was evident. This concerned the adduct (82) formed from tetrafluorobenzene and *t*-butylbenzene which exhibited a PMR spectrum



(82)

at 33° containing a six-proton singlet 12 Hz downfield of a three-proton singlet (Brewer et al. 1967). The splitting was interpreted as a result of a preferred conformation caused by restricted rotation of the t-Bu group as shown in structure (82). The two methyl groups adjacent to the ortho fluorine substituent are presumably deshielded by the aromatic ring to effect their low field position.

The four low temperature examples reported seem more conventional, as at -100° or greater the enormously increased solution viscosities assist the necessary restricted rotation to a significant extent (Cupas and Heyd 1969) in addition to the normal low temperature effect. Anet and his group (1966; 1968) have observed 2:1 t-Bu signal splittings at -160° to -130° in a series of t-Bu cycloalkanes. The separation of the t-Bu singlets were considered

too large to be attributed to ring inversion and the higher field three proton singlet was explained by the Newman diagram in Figure 8. The fully staggered

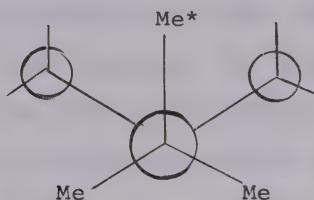


Figure 8. Restricted rotation in t-Bu cycloalkanes.

rotamer was postulated as the preferred conformation at these low temperatures so that the asterisked Me group was more screened by the adjacent ring methylenes than the remaining two methyl radicals. The actual separations of the t-Bu singlets are given below and they can be seen to be of a low order. However, a probable explanation of these order of magnitude is the lack of markedly anisotropic groups (such as phenyl) within these structures; only such strongly magnetic moieties may be expected to produce large splittings.

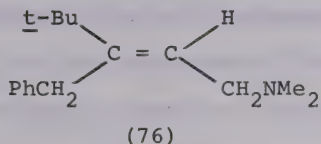
Separation of the t-Bu singlets
in Hz at 60 MHz (solvent, 2:1,
vinyl chloride: CH₂HCl)

n (number of annular
carbon atoms)

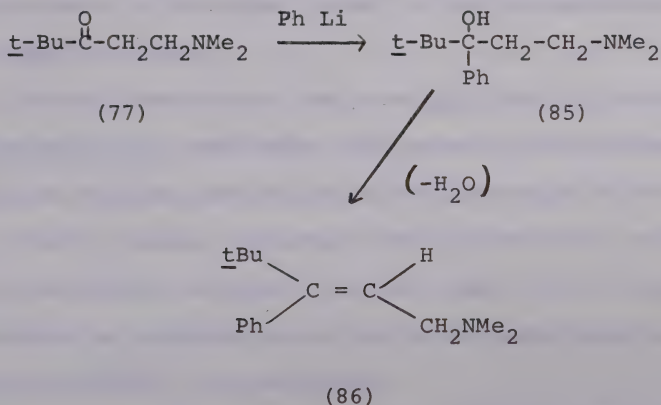
7	5
8	6
11	7
13.5	8
10	9
9	10

t-Bu group into three separate signals in the ratio 1:1:1.

As a continuation of our own work, it was decided to prepare the cis (t-Bu/H) analogue (86) containing a phenyl substituent in place of the benzyl function of compound (76), to examine the effect on the t-Bu resonance absorption and to further our structure:activity studies.



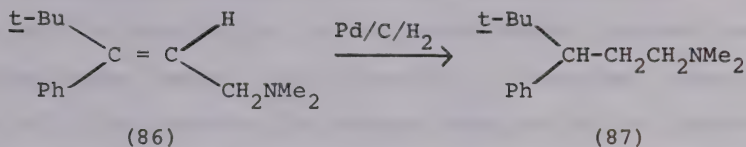
The necessary carbinol (85) was synthesized by reaction of the aminoketone (77) with phenyl-lithium but



samples isolated were heavily contaminated with unchanged ketone and could not be resolved. The alcohol (85) was isolated as a hydrochloride, however, from the product of treating unpurified material from the reaction with an acetic-hydrochloric acid mixture (reflux, 4 hours), together with a 1-t-butyl-3-dimethylamino-1-phenylprop-1-ene. The dehydration procedure allowed equilibration of isomers and hence the product obtained represented the more stable form. Moreover, the PMR spectrum of the total base displayed a single vinylic signal so that only one isomer appeared to be produced. This was probably the cis (t-Bu/H) propene (86) since molecular models (Catalin and Framework) revealed that interactions between adjacent substituents are undoubtedly of a higher order in the corresponding trans (t-Bu/H) isomer.

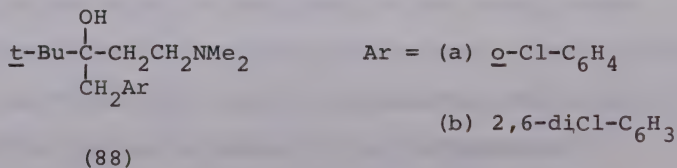
The PMR spectrum of the pure cis (t-Bu/H) prop-1-ene (86) hydrochloride (see Table XII) showed a sharp nine-proton t-Bu singlet indicative of free rotation of this group. Such evidence suggested that the molecular structure of the benzyl analogue (76) was ideal for the requisite restricted rotation situation to produce magnetic non-equivalence within its t-Bu group.

Catalytic hydrogenation of the cis (t-Bu/H) prop-1-ene (86) to the aminopropane (87) was also carried out

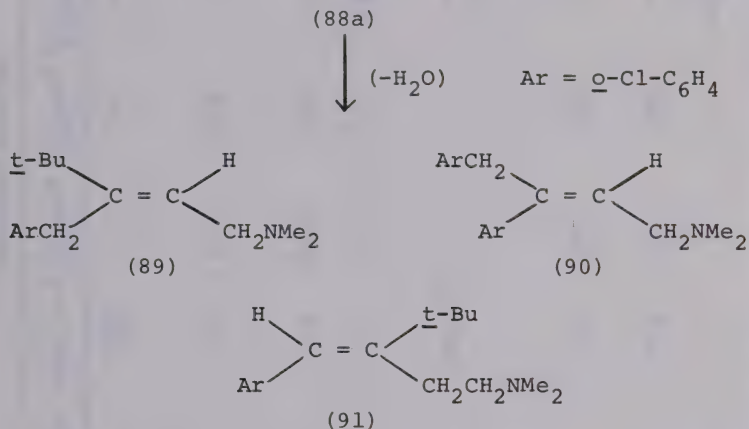


as the t-Bu group in the reduced product appeared to be in a hindered situation on the evidence of models. This made the PMR spectrum of the compound (87) of potential interest but again the t-Bu signal appeared as a sharp nine-proton singlet, indicative of a freely rotating t-Bu group.

It was therefore decided to examine the PMR effects of ortho substitution within the benzyl ring of the cis (t-Bu/H) but-2-ene. To this end, synthesis of the precursor tertiary alcohols (88) was pursued by treatment of the Mannich ketone (77) with the appropriate Grignard reagents. Acid-catalysed elimination of the carbinols was then envisaged to produce the usual aminoalkenic mixtures from which the required cis (t-Bu/H) but-2-enes might be isolated.



The o-chloro carbinol (88a) was obtained in good yield and its dehydration in the normal manner yielded the expected three isomers (89, 90 and 91). Fractional crystallisation of the hydrohalide mixture resulted in the isolation of the three pure isomers (89, 90 and 91) whose PMR



characteristics are entirely comparable (see Table XII) with the corresponding members of the original series. The spectrum of the cis (t-Bu/H) but-2-ene (89) again displayed a two component t-Bu signal and the observed separation was equal to that seen in the phenylbutene example; the absolute chemical shifts were slightly lower field (see Table XII) than in the unsubstituted benzylic compound due to the presence of the electronegative chlorine substituent. It was therefore thought that the o-chloro isomer was still able to adopt the postulated

TABLE XII

PMR CHARACTERISTICS OF VARIOUS t-BUTYLAMINOALKENES

Elimination Substrate	Sample	Compound Number(s) in text	Chemical shifts ^{a,b}				
			C-1 vinyl ^c	C-3 vinyl ^d	CH ₂ Ar ^e	CH ₂ CH ₂ N ^e	t-Bu ^c
OH $\text{t-Bu}-\text{C}(\text{CH}_2\text{Ph})=\text{CH}_2\text{CH}_2\text{NMe}_2$ (78)	total base	(76) (79) (80) (81)	380	337, 305	-	-	120 ^e (3 protons) 69, 62
	<u>cis</u> (t-Bu/H)but -2-ene.HCl	(76)	-	315	161.5	218	111.5 ^e (3 protons) 66.5 (6 protons)
	<u>trans</u> (t-Bu/H) but-2-ene.HCl	(79)	-	352	215	209	157.5 66.5
OH $\text{t-Bu}-\text{C}(\text{CH}_2\text{Ar})=\text{CH}_2\text{CH}_2\text{NMe}_2$ (Ar=O-CI-C ₆ H ₄) (88a)	<u>trans</u> (t-Bu/Ph) but-1-ene.HCl	(81)	392	-	-	164	146 ^g 69.5
	total base	(89) (90) (91)	382	346, ^{g,b}	-	-	131, 119, 112 (3 protons) 71, 63
	<u>cis</u> (t-Bu/H)but -2-ene.HCl	(89)	-	321	172	220	113 ^e (3 protons) 68 (6 protons)
"	<u>trans</u> (t-Bu/H) but-2-ene.HCl	(90)	-	362	215	204	162 68
	<u>trans</u> (t-Bu/Ph) but-1-ene.HBr	(91)	387.5	-	-	163.5	148 72.5

Continued

TABLE XII (Continued)

	C-1 vinyl ^c	C-3 vinyl ^c	C ^d CH ₂ Ar ^e	NCH ₂ CH ^f	CH ₂ CH ₂ N ^e NMe ₂ ^c	t-Bu ^c
OH t-Bu-C-CH ₂ CH ₂ NMe ₂ CH ₂ Ar	(92)	327	186	222	163 ^g	112 ^e (3 protons) 71
(Ar=2,6-diCl-C ₆ H ₃) " (88b)						(6 protons)
OH Ph t-Bu-C-CH ₂ CH ₂ NMe ₂	(93)	349	232	186 ⁱ	154 ^g	74
(85) " (85)	(86)	340 ⁱ	-	-	-	-
cis(t-Bu/H) prop-1-ene.HCl	(86)	357 ^j	-	197 ^k	160 ^g	67

a Chemical shifts in Hz from TMS (internal standard) at an operating frequency of 60 MHz; solvent CDCl₃, coupling constants (J) in Hz.

b Only distinct and unambiguous absorptions quoted.

c Singlet.

d Triplet (J7).

e Broad singlet.

f Doublet (J7).

g Doublet (J5) (^NHMe₂).

h Centre of broad band.

i Deformed triplet.

j C-2 vinylc.

k Doublet of doublets (J = 5 and 7.5).

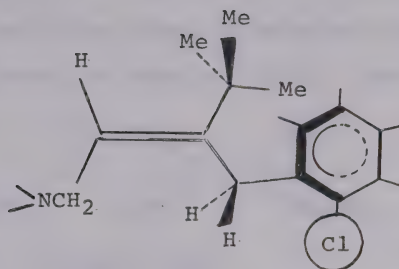
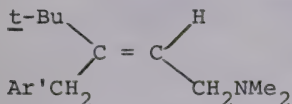


Figure 10. Proposed preferred conformation of the cis (t-Bu/H)-o-chlorobenzyl-aminobut-2-ene (89).

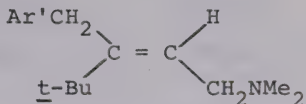
preferred conformation of the benzyl analogue (see Figure 4), possibly by positioning of the large o-chloro substituent in the more remote ortho position (see Figure 10). Furthermore, the increased steric bulk of the substituted aromatic function should augment its non-bonded interactions with the adjacent dimethylaminomethyl group which, in turn, should increase the driving force necessary to place the benzylic function close to the t-Bu group as required for the preferred conformation depicted in Figure 10.

Further work upon this problem involved dehydration of the mixture resulting from reaction between the Mannich base (77) and 2,6-dichlorobenzyl magnesium bromide after failure to isolate a pure sample of the tertiary alcohol (88b) intermediate. Fractional crystallisation of the elimination product provided three aminoalkenes, the yields being low owing to the substantial amount of non-alcoholic

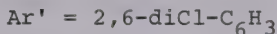
impurity (chiefly 77) contained in the substrate. Two of the products were the isomeric aminobut-2-enes (92 and 93) derived from the carbinol (88b). The third,



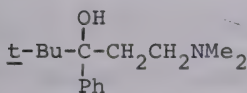
(92)



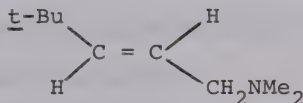
(93)



however, was the aminopropene (86); this unexpected result was corroborated by subsequent isolation of its tertiary alcohol (85) precursor from the total product



(85)



(86)

of the Grignard reaction. Suspicions that the commercial sample of 2,6-dichlorobenzyl bromide used might be contaminated with bromobenzene* which could ultimately be responsible for formation of the carbinol (86), were allayed by the following observations and experiments:

1. Microanalytical figures for carbon and hydrogen agreed very closely with the calculated values for 2,6-dichlorobenzyl

* Chlorobenzene, another possible contaminant, does not undergo the Grignard reaction under normal conditions (Kharasch and Reinmuth 1964; Fieser and Fieser 1961).

bromide as shown below:

		<u>C</u>	<u>H</u>
$C_7H_5BrCl_2$	requires	35.04	2.10
	Found	35.24	1.90

2. Amplified PMR integral values of the aryl:methyl proton signal ratio obtained from a 10% solution of 2,6-dichlorobenzyl bromide gave an observed ratio of 1.49:1 respectively (theoretical 3:2 or 1.50:1). The sensitivity of this PMR method to small amounts of bromobenzene was tested by integral measurements of a series of standard solution of 10% 2,6-dichlorobenzyl bromide mixed with known amounts of bromobenzene (see below).

<u>w/w % PhBr contained in standard solution</u>	<u>Calculated aryl:methyl integral ratio</u>	<u>Observed ratio</u>
0	1.50	1.49
1.3	1.51	1.56
3.6	1.64	1.75
8.5	1.86	1.91
13.6	2.10	2.10

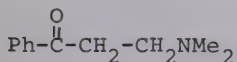
These data showed that, if anything, slightly high values for the observed ratio were obtained so that even 1.3% contamination with bromobenzene was detectable. Thus, this method gave further support for the purity of the bromide substrate.

3. The observed m.p. (55°) of the sample agreed precisely with the value (55°) quoted in the literature (Bertram et al. 1956).

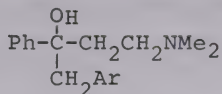
4. The final and most conclusive evidence was provided by a GLC examination of the sample using an F and M Scientific 700 laboratory chromatograph with a hydrogen flame ionisation detector (see experimental for full details). A silicon gum rubber column at 120° was used and a solution of the 2,6-dichlorobenzyl bromide in ether recorded only a single peak for the compound (retention time 20.5 minutes). An analytical sample of bromobenzene was then passed through the column under the same conditions and its retention time was much less (1.2 minutes). Re-examination of the chart for the dichloro compound showed absolutely no trace of any peak at the 1.2 minute mark. Addition of bromobenzene to the pure dichloro solution did, however, provide the expected two peaks at 20.5 and 1.2 minute retention times. The extreme sensitivity of the instrument used, together with the observed results, gave final proof of the high purity (>99%) of the sample of 2,6-dichlorobenzyl bromide used in our experiments.

Thus, reaction between 2,6-dichlorobenzyl magnesium bromide and the aminoketone (77) involves, to some extent, the loss of aryl halogens and the methylene group from the substituted benzyl fragment. This unusual Grignard

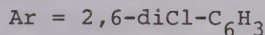
reaction may be linked with the highly hindered nature of the two components of the reaction since the less crowded Mannich base (38), with the same Grignard



(38)



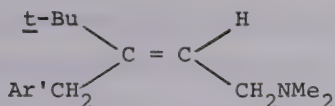
(94)



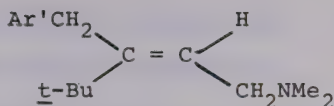
reagent gave a 40% yield of the expected tertiary alcohol (94), no abnormal products being detected. There are few references to the use of 2,6-dichlorobenzyl halides in Grignard reactions (Kharasch and Reinmuth 1954), and the degradative phenomenon noted here appears to be novel. However, the mechanism involved in this unusual cleavage reaction of 2,6-dichlorobenzyl magnesium bromide is obscure.

The configurations of the two isomeric aminobut-2-enes (92 and 93) obtained were based on the differences in the chemical shifts of their vinylic, benzylic methylene, and t-Bu signals, as previously described for the related PhCH_2 and $\text{o-Cl-C}_6\text{H}_4\text{CH}_2$ compounds (76, 79, 89 and 90).

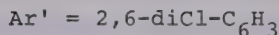
Once again the t-Bu signals differed in a striking manner, that of the trans isomer (93) being a sharp nine-proton while the cis signal was a sharp six plus a broad three proton singlet (see Table XII).



(92)



(93)



As argued before (see p. 86), it is proposed that interactions between the substituted benzyl function and the dimethylaminomethyl substituent cis to it result in the former being deflected towards the t-Bu group. The increase in bulk of the benzylic function following the entry of ortho chloro substituents must render the close approach of the two cis groups correspondingly less favoured and this factor appears to outweigh any increase in the t-Bu/benzylic interaction energy.

Comparison of the benzylic methylene proton resonance positions (see below) for the three cis (t-Bu/H) but-2-enes (76, 89 and 92) showed a progressive and significant

<u>Compound</u>	<u>Benzylic Structure</u>	<u>CH₂ Ar chemical shift</u> <u>in Hz (CDCl₃)</u>
(76) (HCl)	-CH ₂ Ph	161.5
(89) (HCl)	-CH ₂ - <u>o</u> -Cl-C ₆ H ₄	172
(92) (HCl)	-CH ₂ -2,6-diCl-C ₆ H ₃	186

lower field shift as substitution in the ortho aromatic positions increased. At first sight, this apparent increased deshielding effect on the methylene protons indicated that

the greater steric bulk of the aromatic function containing the chloro group(s) was causing progressive tilting of the ring away from the t-Bu group and towards the plane of the carbon-carbon double bond in the postulated preferred conformation (see Figure 4).

This supposition, however, is invalidated by the following two reasons:

1. Magnetic non-equivalence of the t-Bu groups was observed in all three cis (t-Bu/H) compounds (76, 89 and 92). This demonstrated the continuance of the highly hindered situation and the accompanying restricted rotation in each molecule. In addition the chemical shifts of the remote Me signals (three protons) of each t-Bu group were almost unaffected in the unsubstituted (111.5 Hz), o-chloro (113 Hz) and 2,6-dichloro (112 Hz) isomers, which indicated maintenance of the preferred conformation (see Figure 4) in each molecule.
2. Examination of the benzylic methylene chemical shifts of the three benzyl halides used as the Grignard reaction substrates in our studies (see below) showed that the resonance positions of the methylene signals, as chloro substitution in the ortho ring positions increased, fell at lower field just as in the case of the corresponding cis (t-Bu/H) but-2-enes. Thus shifts in the benzyl resonances seen in the aminobutene isomers may be attributed largely to the deshielding effects of the chlorine substituents rather

<u>Halide</u>	<u>CH₂-Ar chemical shift in Hz (CDCl₃)</u>
Benzyl chloride	275
<u>o</u> -chlorobenzyl chloride	283
2,6-dichlorobenzyl bromide	287*

than any effect caused by a change in orientation of the aromatic ring in these structures.

All of the aminoalkenes containing the cyclohexyl, 2-pyridyl and t-Bu groups in the 1- and 2-positions were submitted for pharmacological testing and the data obtained are now discussed.

(ix) PHARMACOLOGICAL RESULTS AND DISCUSSION OF COMPOUNDS DESCRIBED IN (viii)

The pharmacological results obtained for the compounds discussed in section (viii) are given in Table XIII; activity in all cases was low. Each structural type will now be briefly discussed:

1. cis (H/Ph)1-cyclohexyl-4-dimethylamino-2-phenylbut-2-ene (68). This compound possessed the optimal molecular structure for activity amongst aminobutene isomers as previously

* The chemical shifts of the corresponding 2,6-dichlorobenzyl chloride (a better comparative model not to hand) will almost undoubtedly be a few Hz lower field than this value because of the greater inductive effect of chlorine compared to bromine.

TABLE XIII

INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM BY
AMINOALKENES CONTAINING THE CYCLOHEXYL, 2-PYRIDYL AND t-BUTYL GROUPS IN THE 1- OR 2-POSITIONS

Sample	Compound Number in text	Conc. in $\mu\text{g/ml}$	Percentage inhibition at time (in min.)								
			3	6	9	12	15	18	21		
<u>cis</u> (H/Ph)1-cyclohexyl-4-dimethyl- amino-2-phenylbutene.HCl	(68)	0.10	68	30	0	-	-	-	-	-	-
<u>trans</u> -4-dimethylamino-2-phenyl- -1(2-pyridyl)but-1-ene.2HCl	(75)	1.0	97	39	10	0	-	-	-	-	-
"	"	0.50	40	8	-	-	-	-	-	-	-
"	"	0.10	5	0	-	-	-	-	-	-	-
<u>cis</u> -4-dimethylamino-2-phenyl-1- (2-pyridyl)but-1-ene <u>dihydrogen</u> <u>oxalate</u>	(74)	1.0	96	33	8	-	-	-	-	-	-
"	"	0.50	30	0	-	-	-	-	-	-	-
"	"	0.10	9	0	-	-	-	-	-	-	-
Mepyramine standard	(37)	0.001	100	96	79	57	38	27	13	-	-
"	"	"	100	53	16	15	13	-	-	-	-
<u>cis</u> (<u>t</u> -Bu/H)but-2-ene.HCl	(76)	0.01	4	-	-	-	-	-	-	-	-
<u>trans</u> (<u>t</u> -Bu/H)but-2-ene.HCl	(79)	0.10	91	81	64	36	26	24	7	-	-
<u>trans</u> (<u>t</u> -Bu/Ph)but-1-ene.HCl	(81)	0.10	81	50	20	5	-	-	-	-	-
<u>cis</u> (<u>t</u> -Bu/H)prop-1-ene.HCl	(86)	0.01	4	-	-	-	-	-	-	-	-
Mepyramine standard	(37)	0.001	81	50	20	5	-	-	-	-	-
"	"	"	51	4	-	-	-	-	-	-	-

Continued

TABLE XIII (Continued)

Sample	Compound Number in text	Conc. in $\mu\text{g/ml}$	Percentage inhibition at time (in min.)								
			3	6	9	12	15	18	21		
<u>cis</u> (<u>t</u> -Bu/H) <u>o</u> -chlorobut-2-ene.HCl	(89)	0.10	36	30	28	23	-	-	-		
<u>trans</u> (<u>t</u> -Bu/H) <u>o</u> -chlorobut-2-ene.HCl	(90)	0.10	17	12	8	0	-	-	-		
<u>trans</u> (<u>t</u> -Bu/Ph) <u>o</u> -chlorobut-1-ene.HBr	(91)	0.10	49	21	16	11	-	-	-		
Mepyramine standard	(37)	0.001	49	36	27	25	19	15	-		
"	"	"	50	31	28	3	6	0	-		
"	"	"	62	46	24	19	13	0	-		
1(<u>t</u> -Bu)-3-dimethylamino-1-phenyl- propane.HCl	(87)	1.0	53	13	0	-	-	-	-		
Mepyramine standard	(37)	0.001	94	77	47	31	15	0	-		
"	"	"	100	95	73	57	0	-	-		
"	"	"	50	29	18	0	-	-	-		
"	"	"	69	52	38	10	0	-	-		

N.B. In the table, a dash denotes discontinuation of experimental observation.

known from data on 1,2-diarylbutene compounds (see Tables III and VI). The presence of the alicyclic cyclohexyl group in the 1-position sharply reduced antihistaminic activity which suggested that a benzylic aromatic function is a necessary adjunct for blockade of the histamine receptors. Indeed, the latter group may well occupy an additional receptor area which is not implicated in the uptake of histamine itself (see later for speculations in this respect).

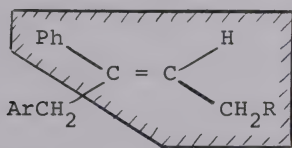
2. 4-Dimethylamino-2-phenyl-1(2-pyridyl)but-1-ene isomers (74 and 75). From previous considerations, both isomers had unfavourable molecular geometries and the low orders of activity observed were therefore as anticipated. Unfortunately, the cis (H/Ph) but-2-ene analogue (with the optimal structure for activity) was not isolated so that the effect of having a 2-pyridyl benzylic function could not be tested.

3. t-Butylaminoalkenes. All the various isomers tested had feeble antihistaminic properties with the exception of the trans (t-Bu/H) but-2-ene (79) which had moderate activity at a fairly high solution concentration (0.10 µg/ml). Both cis (t-Bu/H) but-2-enes (76 and 89) tested had sharply reduced potencies compared to the parent cis diphenyl but-2-ene (33) compound. These data emphasised the need for an aromatic function in the 2-position of cis but-2-enes (rather than merely a bulky group) which suggested that the coplanar 2-aryl function was an important factor for

uptake by the histamine receptors.

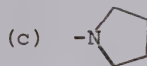
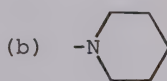
At this point, it seems pertinent to summarize all the conclusions reached from the pharmacological results for the various aminobutene isomers described and discussed in Chapter 3 of this thesis:

1. The most important deduction to emerge from the pharmacological data is that the molecular geometry of cis (H/Ph)1,2-diaryl butenes (58) is optimal for anti-histaminic potency amongst aminobutene isomers.



(58)

R = (a) NMe_2



2. The 1,2-aromatic functions of these most potent isomers (58) appear necessary for activity and the planar region (see shaded area of 58) of these molecules is considered essential for significant interaction with the histamine receptors.

3. The high activities of the dimethylamino (33), pyrrolidino (47) and piperidino (41) cis (H/Ph) but-2-enes indicates that the nature of the basic group (R) amongst these most active aminobutene isomers (58) is not too critical. There is some evidence, however, that the N-pyrrolidino tertiary amino function is associated with the highest

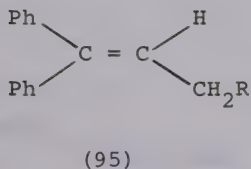
orders of potency which may possibly be due to superior transport characteristics of isomers containing this basic group.

CHAPTER 4

3-AMINOPROPENES AND RELATED COMPOUNDS RESULTS AND DISCUSSION

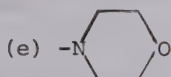
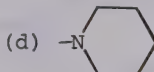
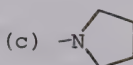
(i) HISTORICAL INTRODUCTION

In 1949, Adamson prepared a series of 4-amino-1-diphenylprop-1-enes (95) which were shown to possess



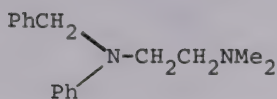
R = (a) NMe_2

(b) NEt_2

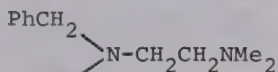


only moderate antihistaminic potencies (Green et al. 1951). However, during the previous year, Huttner (1948) had observed that replacement of the phenyl group by 2-pyridyl in several known antihistamines increased activity. For example, substitution of the N-phenyl group of Antergan (24), led to the more potent drug Pyribenzamine (96) which, in turn, led to the introduction of the clinically useful antihistamine, Mepyramine (37).

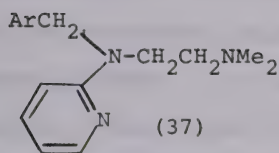
Accordingly, Adamson and Billingham (1950) prepared 2-pyridyl analogues of the diphenylprop-1-enes, by dehydration of the appropriate tertiary alcohols (97). The amino-propene products were separated as the pure cis and trans isomers and one compound, the trans (2-pyridyl/ CH_2N) prop-1-ene (12), was found to be extremely potent; most significantly, it was about 80 times more active than the related



(24)

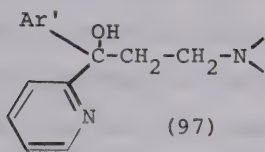


(96)

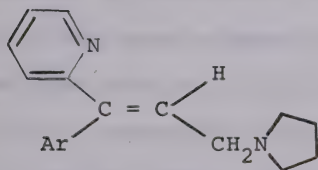


(37)

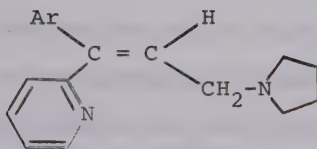
(Ar = p-MeO-C₆H₄)



(97)



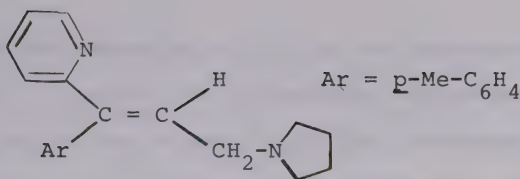
(12)



(13)

(Ar = p-Cl-C₆H₄)

cis isomer (13) (Adamson et al. 1951). Further examples of 2-pyridyl aminopropenes were then prepared (Adamson et al. 1957) and the most active member of the series was found to be the trans (2-pyridyl/CH₂N) prop-1-ene (14) (Green 1953b) later marketed as the antihistamine Triprolidine.



(14)

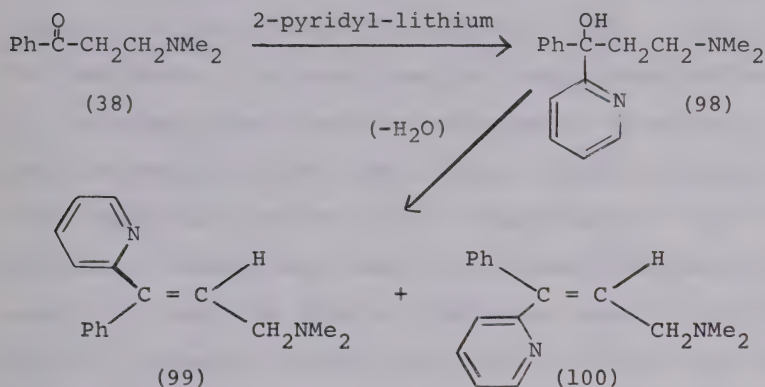
Apart from the three isomers (12, 13, and 14) discussed above, no pharmacological data for any of the other aminopropenes prepared were reported by either Adamson or Green. It was therefore decided to synthesise examples of the Triprolidine type together with some suitably substituted Me derivatives from two standpoints:

1. To examine the previously undetermined PMR spectra of pure isomers in an attempt to make configurational assignments by the same arguments used for the aminobutene series (see Section 2). If the PMR method proved successful, it was intended to check the configurations based on UV assigned to several isomers by Adamson and his group (1951; 1957; 1958).
2. To obtain our own pharmacological data for various aminopropene isomers so that a full stereochemical structure: activity study of these compounds could be made.

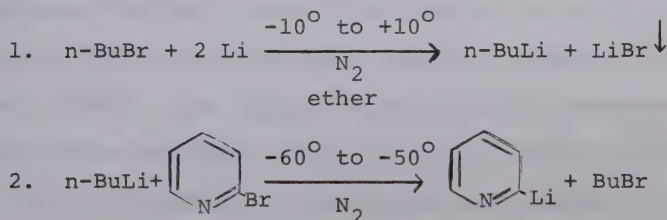
(ii) PREPARATION OF 3-AMINO-1-ARYL-1-(2-PYRIDYL)PROP-1-ENE ISOMERS

The dimethylamino isomers (99 and 100) were initially prepared using the method of Adamson and Billingham (1950)

who had reported easy separation of the two compounds by fractional crystallisation or ion-exchange chromatography. 2-Pyridyl-lithium was the reagent used for introduction of the 2-pyridyl group into the carbinolic structure (98) and



its synthesis was by the two stages shown below. These consisted of the preparation of an ethereal solution of n-butyl-lithium (we used the improved method of Akhtar and Barton, 1964, for this step) followed by its treatment with



2-bromopyridine under nitrogen at -60° to -50° . During the course of the second stage, great care was taken to ensure continual maintenance of the reaction temperature

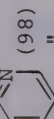


below -45° as Adamson and Billingham (1950) had reported an explosion after one of their preparations had warmed above this temperature.

Dehydration of the alcohol (98) was effected by heating in a solution of 85% sulphuric acid at $100-110^{\circ}$ for two hours. The basic reaction product was isolated in the normal manner and its PMR spectrum revealed two methyleneamino doublets and a single vinylic triplet. This suggested that the vinylic absorptions for the two free base isomers were coming to resonance at exactly the same field position (a point confirmed later). Acidification of the basic mixture with ethanolic oxalic acid and subsequent fractional crystallisation yielded pure oxalate salts of each isomer; their PMR spectra were determined in D_2O and the characteristics observed are shown in Table XIV.

Configurational assignments of the two oxalate isomers were initially made from observation of their UV spectra in ethanol using the method of Adamson and his group (1957). The trans (2-pyridyl/ CH_2N) compound (99) exhibited absorption maxima at 245 (ϵ 7800) and 283 m μ (ϵ 5690) to produce a UV spectrum very similar to that of 2-vinylpyridine (101), whereas the cis (2-pyridyl/ CH_2N) isomer (100) exhibited a single band (λ_{max} 252 m μ , ϵ 10,000) typical of styrene (102). Adamson and his group obtained

TABLE XIV

SPECTRAL CHARACTERISTICS OF SOME 3-AMINO-1-ARYL-1-(2-PYRIDYL)PROP-1-ENE ISOMERS

Elimination Substrate	Sample	Compound Number in Text	Chemical shifts ^a		$\lambda_{\max}(\epsilon)^g$
			Vinylic ^c	Others	
OH Ph-C-CH ₂ CH ₂ NMe ₂  (98)	trans(2-pyridyl)/CH ₂ N) prop-1-ene oxalate ^b	(99)	398 (J7.5)	232 (J7.5) NMe ₂ 167 ^e	245 (7800) 283 (5700)
"	free base from above oxalate ^f	(99)	380 (J7)	183 (J7) NMe ₂ 136 ^e	-
"	cis(2-pyridyl)/CH ₂ N) prop-1-ene oxalate ^b	(100)	382 (J7.5)	226 (J7.5) NMe ₂ 169 ^e	252 (10000)
"	free base from above oxalate ^f	(100)	380 (J7)	190 (J7) NMe ₂ 135.5 ^e	-
OH Ar-C-CH ₂ CH ₂ -N-  Ar=  (104)	trans(2-pyridyl)/CH ₂ N) prop-1-ene oxalate ^b	(14)	399 (J7)	241 (J7) ArMe 146 ^e	238 (14700) 283 (6650)
"	free base from above oxalate ^f	(14)	Submerged in 192.5 Aryl signal (J7) ArMe 142 ^e		-
"	cis(2-pyridyl)/CH ₂ N) prop-1-ene oxalate ^b	(106)	387 (J7.5)	237 (J7.5) ArMe 143 ^e	258 (14500) 244 (14100)
"	free base from above oxalate ^f	(106)	376 (J7.5)	194.5 (J7.5) ArMe 136.5 ^e	-

^a Chemical shifts in Hz from DSS or TMS (internal standard) for D₂O or CDCl₃ solutions respectively (see b) at an operating frequency of 60 MHz; coupling constants (J) in Hz.

^b D₂O solution.

^c Triplet.

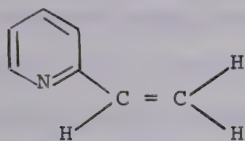
^d Doublet.

^e Singlet.

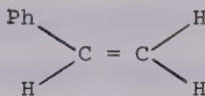
^f CDCl₃ solution.

^g Solvent EtOH; λ_{\max} is wavelength in mμ; extinction coefficient (ε) shown in parenthesis.

comparable UV parameters for these compounds and interpreted their results according to the relative spatial positions of the aromatic functions about the olefinic bond. In the trans isomer (99) non-bonded interactions



(101)



(102)

between the adjacent phenyl and dimethylaminomethyl groups twists the aryl ring out of the plane of the double bond to obliterate the chromophoric effect of the styrenoid portion of the molecule. At the same time, the 2-pyridyl function remains essentially coplanar with the double bond to constitute a system of extended conjugation much akin to the conjugated section of the 2-vinyl pyridine molecule. Thus, there is a distinct resemblance between the UV spectra of the trans isomer (99) and the 2-vinyl pyridine (101) model. Similarly, within the cis isomer (100), only the phenyl ring and carbon-carbon double bond may be coplanar. Thus the UV spectrum of the cis isomer strongly resembles that of styrene (102).

Having determined the configurations of the two isomers (99 and 100) by the UV method it now remained to consider and explain the appropriate PMR absorptions of each compound. In this context, knowledge of the comparative

deshielding effects of the 2-pyridyl and phenyl aromatic functions was required; the order of these effects was obtained by observation of the respective chemical shifts of the vinylic protons cis to the aromatic functions of the same two model systems, 2-vinylpyridine (101) and styrene (102), used for the UV assignments. Within these compounds, the 2-pyridyl and phenyl rings are in uncrowded molecular environments so that each cis vinylic shift position reflects the time-averaged deshielding influence upon it by the adjacent aromatic function. The literature values for the cis vinylic signals in CDCl_3 of 2-vinyl pyridine and styrene are 373 (Bhacca et al. 1962) and 337 Hz (Tobey 1969) respectively from TMS at 60 MHz. Thus, a sterically uncrowded 2-pyridyl function appears to have a more significant deshielding effect than a phenyl ring upon a group cis to it within an olefinic structure.

The observed PMR values for the two isomers in the free base and oxalate states are given in full in Table XIV and the chemical shifts for the methyleneamino and vinylic protons are also shown below. The relative field positions of each isomeric group will now be discussed:

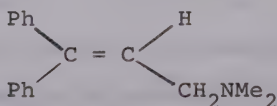
Compound	Form	Chemical Shifts in Hz	
		<u>CH₂N</u>	<u>=C-H</u>
<u>trans</u> (2-pyridyl/CH ₂ N) (99)	base ^a	183	380
"	oxalate ^b	232	398
<u>cis</u> (2-pyridyl/CH ₂ N) (100)	base ^a	190	380
"	oxalate ^b	226	382

^a in CDCl₃ (TMS)

^b in D₂O (DSS)

1. Vinylic Signals. In the two oxalate isomers the chemical shifts are in the expected order i.e. the vinylic shift of the trans (2-pyridyl/CH₂N) isomer (99) is lower field than the cis compound (100). This is probably due to the greater deshielding effect of the 2-pyridyl function on its adjacent group in the trans compound.

The vinylic shifts of the free base isomers are precisely the same (380 Hz), however, but the field position for the cis (2-pyridyl/CH₂N) compound is rather low when compared to the value of 371 Hz (also in CDCl₃) for the vinylic proton of the model compound (95a) (described later). The diphenyl analogue (95a) should be a suitable comparative



(95a)

model as its vinylic proton is in a very similar molecular environment. It therefore appears that the free base vinylic shift of the cis isomer (100) in CDCl_3 is anomalous (see p. 126 for further discussion on this point).

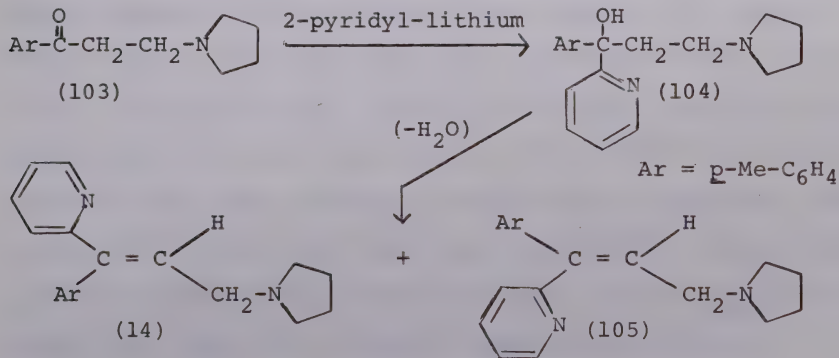
2. Methyleneamino Signals. The appropriate shifts of the free base compounds are in the predicted order from consideration of the relative deshielding influences of the adjacent aromatic functions, but the separation of the cis and trans signals is only small (7 Hz).

The shifts of the oxalate isomers, however, are in the opposite order to that of the free base compounds. It therefore seems probable that solvation effects of the D_2O medium are altering both the electronic and bulk properties of the two N centres. Furthermore, in solution only the dimethylamino function is positively charged as it is known that the pK_a 's for isomers of this type are approximately 9.5 for the aliphatic amino group and only 3.0 for the 2-pyridyl centre (Adamson et al. 1957).

It is therefore postulated that in the cis(2-pyridyl/ CH_2N) isomer (100) the adjacent solvated N structure features sterically interact to force the 2-pyridyl ring significantly out of the plane of the double bond. Hence, the overall effect may be to produce a slight screening influence on the methyleneamino group in spite of its juxtaposition with the 2-pyridyl ring. The methyleneamino

signal of the cis (2-pyridyl/CH₂N) oxalate isomer (100) therefore comes to resonance at higher field than the corresponding absorption for the trans (2-pyridyl/CH₂N) compound (in the free bases, the cis methyleneamino signal is 7 Hz lower field than the corresponding trans signal). In the latter isomer, it is proposed that steric clashing between the adjacent phenyl and methyleneamino groups is of a less serious order; the phenyl ring remains more closely in the plane of the double bond so that the adjacent methyleneamino protons are more effectively deshielded.

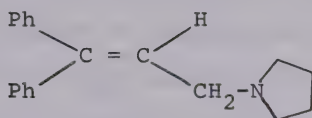
Thus, PMR spectroscopy appeared to provide a suitable method for configurational assignments of 2-pyridyl propene isomers. A further check of the technique was provided by examination of the PMR spectra of Triprolidine (14) and its cis (2-pyridyl/CH₂N) isomer (105). These compounds were synthesized by dehydration of the appropriate carbinol (104) after the latter had been prepared



by reaction of the Mannich ketone (103) with 2-pyridyl-lithium. Dehydration with 85% sulphuric acid at 100-110° for a two hour period gave only one product (14) which was presumably the thermodynamically more stable isomer. Kinetic control of the elimination reaction was achieved, however, by use of a fifteen minute heating time which yielded approximately equal amounts of the two isomers (14 and 105) (PMR evidence). The unique effect of the p-tolyl group to bring dehydration reactions rapidly to equilibrium has been previously noted by Beckett and co-workers (1967) during their study of a series of tetrahydropyridines.

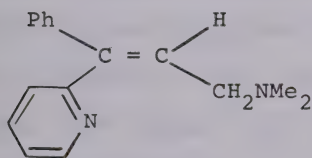
Fractional crystallisation of the oxalate mixture led to the isolation of pure oxalate salts of both Triprolidine (14) and its cis isomer (105). As before, configurations were based on the UV characteristics and relative field positions of the vinylic proton shifts of the pure oxalate isomers. The field positions of the methyl-amino doublets of each compound were again in the reverse order (see p. 123) in the free base and oxalate forms. Moreover, the vinylic shift (376 Hz) of the cis free base (105) agreed very well with the value of 377.5 Hz for the vinylic proton of the model diphenyl analogue (95c) (described later). This shift for the cis isomer was significantly higher field than the corresponding submerged signal for the trans compound (see Table XIV), a result which emphasizes the

anomalous nature of the vinylic chemical shift of the

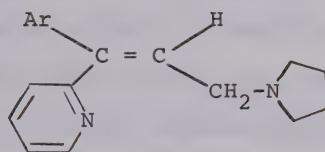


(95c)

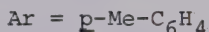
cis (2-pyridyl/CH₂N) dimethylamino free base (100) (see p. 123). The latter phenomenon may now be explained by the differences in steric bulk of the two amino functions of the related cis compounds; the deshielding effect of an uncrowded 2-pyridyl group upon a function trans to it



(100)



(105)



appears to be significant when the respective trans vinylic shifts of 327 (Bhacca et al. 1962) and 308 Hz (Tobey 1969) (from TMS) of the model 2-vinylpyridine (101) and styrene (102) compounds are compared; this observation contrasts to the negligible deshielding effect of a trans phenyl ring (Tobey 1969).

It is therefore proposed that the trans deshielding influence of the 2-pyridyl group on the vinylic proton of the cis dimethylamino free base (100) is of significance

inspite of some twisting by the heterocyclic function out of the plane of the double bond; accordingly, the vinylic shift is reduced to an apparently anomalous low field position (in the cis oxalate this effect is much reduced due to the increased bulk of the solvated 2-pyridyl group). In the cis pyrrolidino free base (105) the greater non-bonded interactions between the 2-pyridyl ring and the bulkier basic function are considered to minimise the trans deshielding effect upon the vinylic proton because of the increased lack of coplanarity of the 2-pyridyl ring with the double bond. This concept is further supported by the very small (+0.2 Hz) separation of the cis and trans methylene amino signals of the free base compounds. Thus, the vinylic shift of the cis isomer agrees very closely with that of the model diphenylpyrrolidino compound (95c).

The order of vinylic shifts of the free base isomers was therefore the same as for the oxalate isomers; both forms were now in accord with arguments based on the proposed relative deshielding effects of the 2-pyridyl and phenyl functions upon adjacent groups within aminopropene molecules.

Finally, the four pure aminopropene isomers (99, 100, 14 and 105) were submitted for pharmacological evaluation to assess the importance of the stereochemical features of these compounds in determining their antihistaminic properties.

(iii) PHARMACOLOGICAL RESULTS AND DISCUSSION OF THE
3-AMINO-1-ARYL-1-(2-PYRIDYL)PROP-1-ENE ISOMERS

The pharmacological data obtained are given in Table XV and the cis and trans dimethylaminopropenes (99 and 100) had only feeble antihistaminic activities of short duration. In addition, there was no significant difference in the activities of these two compounds but in the case of the Triprolidine isomers (14 and 105) the trans (2-pyridyl/CH₂N) compound (14) (Triprolidine oxalate) was markedly more potent than its cis isomer (105). The pA₂ value for the trans isomer (14) was determined as 9.0 indicating its extreme antihistaminic activity as might be expected of a drug in current clinical use.

However, it is clear that our own pharmacological results do not wholly support the contention of Adamson and his group (1951) that high and specific antihistaminic activity is shown only by the isomers with the trans (2-pyridyl/CH₂N) configuration. A firm conclusion on this point could only be obtained by the testing of a large number of aminopropene isomer pairs containing various basic and aryl functions.

Nevertheless, we continued our study of aminopropenes containing the 2-pyridyl group by synthesizing some analogues containing Me substituents to examine the effect on activity of increased non-planarity within these structures.

INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM BY

SOME 3-AMINO-1-ARYL-1-(2-PYRIDYL)PROP-1-ENE ISOMERS

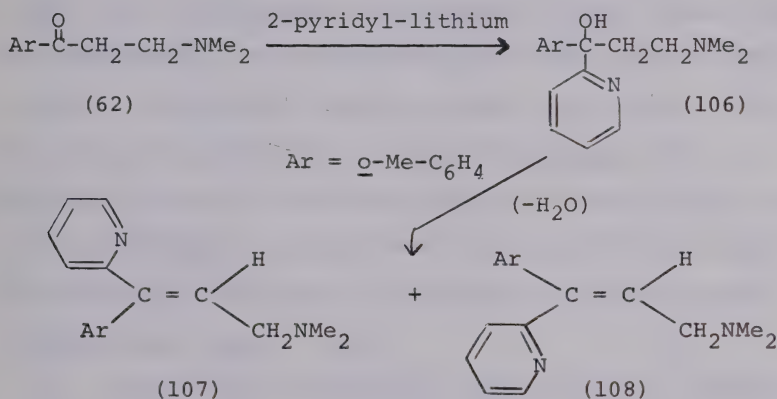
Sample	Compound Number in text	Conc. $\mu\text{g/ml}$	Percentage inhibition at time (in min.)									
			3	6	9	12	15	18	21	24		
trans(2-pyridyl/CH ₂ N)-3-(1-pyrrolidino)-1-p-tolylprop-1-ene oxalate	(14)	1.0	100	100	72	83	63	-	-	-		
"	"	0.01	59	45	24	14	0	-	-	-		
cis(2-pyridyl/CH ₂ N)-3-(1-pyrrolidino)-1-p-tolylprop-1-ene oxalate	(105)	1.0	61	54	25	29	25	21	18	11		
Mepyramine standard	(37)	0.001	50	32	22	15	10	9	4	-		
"	"	"	66	33	23	9	4	-	-	-		
trans(2-pyridyl/CH ₂ N)-3-dimethyl-amino-1-phenylprop-1-ene oxalate	(99)	0.10	32	30	23	0	-	-	-	-		
cis(2-pyridyl/CH ₂ N)-3-dimethyl-amino-1-phenylprop-1-ene oxalate	(100)	0.10	40	32	0	-	-	-	-	-		
Mepyramine standard	(37)	0.001	49	36	27	25	19	15	-	-		
"	"	"	50	31	28	3	6	0	-	-		
"	"	"	62	46	24	19	13	0	-	-		

N.B. In this table, a dash denotes discontinuation of experimental observation.

(iv) 3-AMINO-1-ARYL-1(2-PYRIDYL)PROP-1-ENES CONTAINING METHYL GROUPS

(a) o-Tolyl Derivatives

The o-tolyl carbinol (106) was prepared in low yield (11%) from 2-pyridyl-lithium and the appropriate Mannich ketone (62). Acid-catalysed elimination of the carbinol in 85% sulphuric acid at 100-110° for 2.5 hours



yielded a mixture of 65% of the trans (2-pyridyl/CH₂N) (107) and 35% of the cis (2-pyridyl/CH₂N) (108) amino-propenes (PMR integral data). Both compounds were novel and acidification of the basic product with ethanolic oxalic acid followed by fractional crystallisation yielded one isomer in the pure oxalate form. Its related isomer could not be resolved but PMR spectra of the pure compound and a mixed oxalate crop (see Table XVI) gave comparative



spectral parameters of the two isomers. The vinylic signal of the pure oxalate came to resonance at much lower field (409.5 Hz) than the same signal (363 Hz) for the other isomer contained in the mixture. The large cis/trans vinylic shift difference was explained by the assignment of the trans (2-pyridyl/CH₂N) (107) configuration to the pure compound (confirmed by the UV spectrum of this isomer being of the 2-vinylpyridine type, see experimental). Within the latter isomer there is undoubtedly a strong deshielding effect by the 2-pyridyl ring on the adjacent vinylic proton; the similar effect by the o-tolyl function in the related cis isomer is greatly reduced by the non-planarity of the o-tolyl and vinylic groups as a result of their steric interaction (evidence of models and UV evidence of related o-tolyl aminobutenes; see p. 66).

Liberation of the bases from the mother liquors and re-acidification with ethanolic hydrogen bromide led to the isolation of a 50:50 dihydrobromide mixture of the two isomers, but a pure sample of the cis (2-pyridyl/CH₂N) isomer (108) could not be obtained.

PMR spectral data for the two isomers (the values for the cis isomer being obtained from the mixtures) are given in Table XVI. In contrast to the phenyl analogues (99 and 100), the methyleneamino signals for the trans isomer (107) are at higher field (225.5 and 172 Hz) than

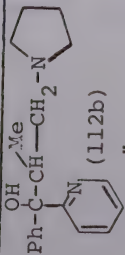
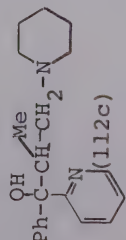
TABLE XVI

PMR CHARACTERISTICS OF 3-AMINO-1-ARYL-1-(2-PYRIDYL)PROP-1-ENES CONTAINING METHYL GROUPS

Elimination Substrate	Sample	Compound Number in text	Chemical shifts ^a		
			Vinyllic ^c CH ₂ N	=C-Me ^e	Miscellaneous
$\text{Ar}-\text{C}(\text{OH})=\text{CH}-\text{CH}_2\text{NMe}_2$  (106)	<u>trans</u> (2-pyridyl)/CH ₂ N prop-1-ene oxalate ^{b,2}	(107)	409.5 (J7.5)	225.5 ^d (J7.5)	- ArMe 117 ^e , NMe ₂ 169 ^e
	<u>trans</u> (2-pyridyl)/CH ₂ N prop-1-ene.2HBr ^{b,2}	(107)	426.5 (J7.5)	238 ^d (J7.5)	- ArMe 127 ^e , NMe ₂ 178 ^e
	free base from above salts ^g	(107)	412 (J7)	172 ^d (J7)	- ArMe 124 ^e , NMe ₂ 132.5 ^e
	<u>cis</u> (2-pyridyl)/CH ₂ N prop-1-ene oxalate ^{b,f}	(108)	362 (J7.5)	236 ^d (J7.5)	- ArMe 114 ^e , NMe ₂ 172.5 ^e
	<u>cis</u> (2-pyridyl)/CH ₂ N prop-1-ene.2HBr ^{b,f}	(108)	390.5 (J7.5)	253.5 ^d (J7.5)	- ArMe 125 ^e , NMe ₂ 181.5 ^e
$\text{Ph}-\text{C}(\text{OH})(\text{Me})=\text{CH}-\text{CH}_2\text{NMe}_2$  (112a)	free base from above salts ^{f,g}	(108)	359 (J7)	205 ^d (J7)	- ArMe 122 ^e , NMe ₂ 136 ^e
	<u>trans</u> (2-pyridyl)/CH ₂ N prop-1-ene oxalate ^{b,f}	(113)	-	223 ^e	110.5 NMe ₂ 166 ^e
	free base from above oxalate ^g	(113)	-	148 ^e	114 NMe ₂ 130 ^e
	<u>cis</u> (2-pyridyl)/CH ₂ N prop-1-ene oxalate ^b	(114)	-	232 ^e	108 NMe ₂ 163 ^e
	free base from above oxalate ^g	(114)	-	178 ^e	111.5 NMe ₂ 128 ^e

Continued

TABLE XVI (Continued)

CH_2N	$=\text{C-Me}^e$		
	(115)	-	230 ^e 113.5
"	(115)	-	176.5 ^e 116.5
"	(116)	-	238 ^e 113.5
"	(116)	-	190.5 ^e 115
	(117), (118)	-	222 ^h , 232 ^h 113 ^h
"	(117), (118)	-	225 ^h , 213.5 ^h 110, 111
"	(117), (118)	-	177 ^e 112
"	(117), (118)	-	188 ^e , 182 ^e 127, 121

a Chemical shifts in Hz from DSS or TMS (internal standards) for D₂O or CDCl₃ solutions respectively (see b) at an operating frequency of 60 MHz; coupling constants (J) in Hz.

b D₂O solution.

c Triplet.

d Doublet.

e Singlet.

f Data obtained from spectra of mixtures of both isomers.

g CDCl₃ solution.

h Broad singlet.

j DMSO-d₆ solution (TMS internal standard).

k C₆H₆ solution. (TMS internal standard).

the corresponding absorptions (236 and 205 Hz) in the cis isomer (108) in both the oxalate and free base forms, respectively. These observations can be attributed to the serious steric clashing between the adjacent o-tolyl and methyleneamino groups contained in the trans (2-pyridyl/CH₂N) (107) isomer. Molecular models (Catalin and Framework) of the trans isomer suggest that the o-tolyl ring preferentially orientates itself at an angle of about 90° to the plane of the carbon-carbon double bond. Thus, there is a distinct screening effect by the aromatic function on the cis methyleneamino protons which therefore resonate at high field. In the cis (2-pyridyl/CH₂N) (108) isomer, the adjacent solvated N functions do not interact so markedly as the o-tolyl/methylamino situation of the other isomer. Hence the 2-pyridyl ring is disposed at an angle of significantly less than 90° to the double bond which results in the methylamino absorption of the cis isomer being lower field than the corresponding signal of the trans isomer.

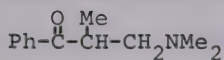
The PMR authenticated trans (2-pyridyl/CH₂N) isomer and the 50:50 mixture of both isomers (107 and 108) were submitted for antihistaminic evaluation. The pharmacological results obtained are given in Table XVII and are discussed in section (iv).

(b) 2-Methyl Derivatives

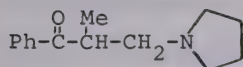
It was decided to prepare several 2-Me aminopropene derivatives as models indicated serious disturbances as a result of both Aryl/Me and Aryl/CH₂N steric clashing. Such interactions caused the UV spectra of these isomers to appear as hybrids of both the 2-vinylpyridine and styrenoid types which rendered the method unsuitable for configurational assignments (Adamson et al. 1957).

It was anticipated that the complexity of the steric interactions within these molecules would make utilisation of the comparative PMR characteristics of various isomers difficult for configurational assignments. Nevertheless, it was hoped that several previous configurational assignments (based on order of elution from ion-exchange columns and magnitudes of m.ps.) made by Adamson and his group (1957) might be checked by appropriate application of PMR spectral parameters.

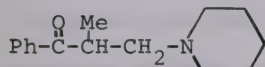
These tertiary alcohols of structure (112) were prepared from the appropriate Mannich ketones (109, 110 and 111) and 2-pyridyl-lithium. The PMR spectra of each of the three alcohols suggested that they were pure diastereoisomers (no duplication of signals) of the same configuration (see below for similarity of Me shifts).



(109)

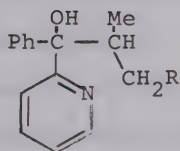


(110)



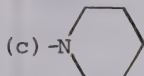
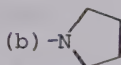
(111)

2-pyridyl-lithium



(112)

R = (a) NMe₂



<u>Tertiary Alcohol</u>	<u>Chemical shift in Hz (from TMS) of Me signal of free base in CDCl₃</u>
-------------------------	--

112a	59 (J7)
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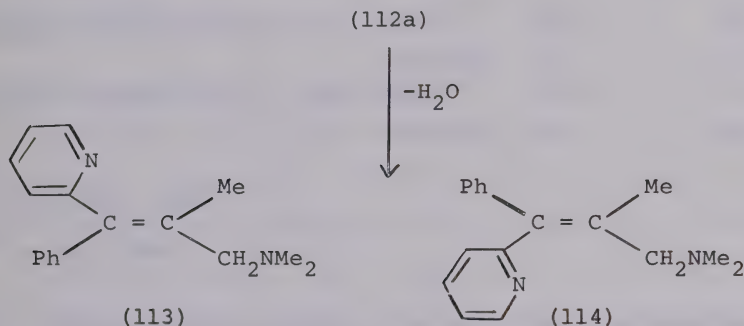
112b	56 (J7)
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112c	58 (J7)
------	---------

(N.B. All other group shifts were masked in the pyrrolidino and piperidino carbinols)

Each carbinol was therefore designated with an arbitrary α -notation. Examination of the mother liquors of each preparation showed no sign of the β -diastereoisomer (only unchanged ketone precursor) which indicated a stereospecific reaction mechanism for formation of the alcohols.

Dehydration of the novel dimethylamino carbinol (112a) by the usual method yielded an approximately equal mixture of both isomers (113 and 114). Their presence was



shown by the appearance of two signals in both the olefinic Me and dimethylamino resonance regions of the basic product. Fractional crystallisation of the oxalate salts yielded a pure isomer which was tentatively assigned the cis (2-pyridyl/ CH_2N) configuration (114). The second isomer could not be resolved but a mixed oxalate was obtained which was considerably enriched (70% from integral data) with this compound.

Inspite of the complex steric interactions within the two isomers an attempt has been made to make tentative configurational assignments. The PMR values for the groups used for assignment of configurations are shown below and a brief discussion of the arguments used now follows:

<u>Compound</u>	<u>Form</u>	Chemical shifts in Hz	
		<u>CH₂N</u>	<u>=C-Me</u>
<u>trans</u> (2-pyridyl/CH ₂ N) (113)	base ^a	148	114
" "	oxalate ^b	223	110.5
<u>cis</u> (2-pyridyl/CH ₂ N) (114)	base ^a	178	111.5
" "	oxalate ^b	232	108

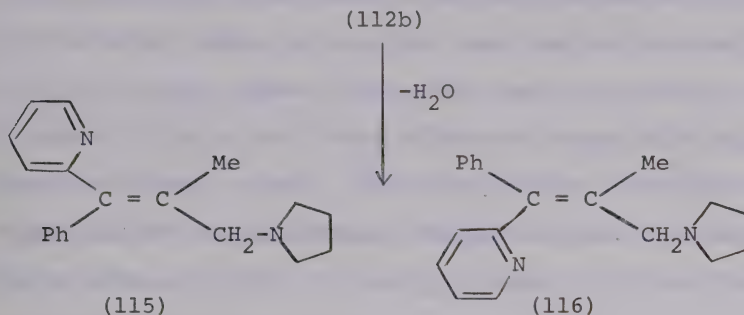
^a in CDCl₃ (TMS)

^b in D₂O (DSS)

1. Methyleneamino Signals. In both the free base and oxalate forms the methyleneamino signals of the cis (2-pyridyl/CH₂N) isomer (114) are considered to fall at lower field than the corresponding shifts for the trans compound because of their close molecular proximity to the 2-pyridyl ring. The latter heterocyclic function is considered (see p. 120) to have a greater deshielding influence than the phenyl ring.

2. Olefinic Me Signals. The observed trend of the isomeric Me signals is also in accord with the proposed relative deshielding effects of the adjacent aromatic functions.

Elimination of the pyrrolidino carbinol (112b) yielded a mixture of the two isomers (115 and 116) as



shown by the duplication of olefinic Me and methylene-amino signals in the PMR spectrum of the basic product. Fractional crystallisation of the oxalates only led to the isolation of a mixture of 85% of one isomer and 15% of the other compound (PMR integral data). Differences in chemical shifts of the characteristic absorptions of the two isomers were not very marked and the olefinic Me shifts of the isomeric oxalates were identical (see below).

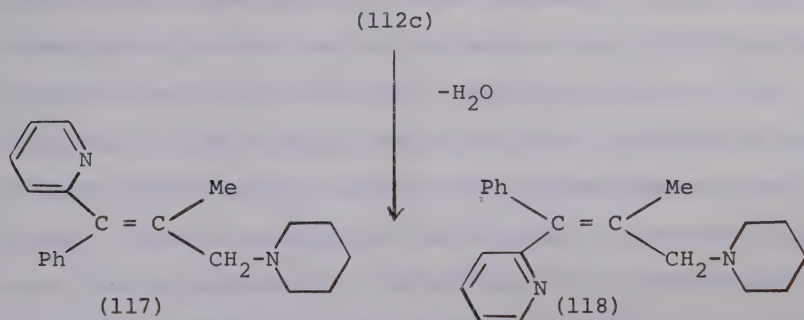
<u>Compound</u>	<u>Form</u>	<u>Chemical shifts in Hz</u>	
		<u>CH₂N</u>	<u>=C-Me</u>
<u>trans</u> (2-pyridyl/CH ₂ N) (115)	base ^a	176.5	116.5
"	oxalate ^b	230	113.5
<u>cis</u> (2-pyridyl/CH ₂ N) (116)	base ^a	190.5	115
"	oxalate ^b	238	113.5

^a in CDCl₃ (TMS)

^b in D₂O (DSS)

However, tentative assignments to the major and minor components of the enriched mixture were made; the higher field olefinic Me and lower field methyleneamino signals of the major isomer as the free base led to its designation as the cis isomer (116) after again considering the 2-pyridyl ring to be a more effective deshielding agent than the phenyl moiety. Thus the mixture (subsequently submitted for antihistaminic evaluation) was considered to be composed of 85% of the cis isomer (116) and 15% of the trans compound (115).

Acid catalysed dehydration of the piperidino carbinol (112c) over a period of two hours yielded a basic product which exhibited only single signals for the olefinic Me (112 Hz from TMS) and methyleneamino (177 Hz) groups in



CDCl₃. Each signal appeared as a sharp singlet which suggested that equilibration had occurred with the formation of the thermodynamically most stable compound.

The elimination was therefore repeated using a fifteen minute heating period but the PMR spectrum of the product was unchanged. Formation of the oxalate salt and numerous recrystallisations led to a compound with a constant m.p. so that stereospecific dehydration of the alcohol (112c) to form a single isomer appeared to have occurred. However, the PMR spectrum of the oxalate in D_2O showed two methyleneamino signals at 222 and 232 Hz (from DSS) apart from a single broad Me singlet at 113 Hz. An additional spectrum of the sample in $DMSO-d_6$ showed the presence of two separate Me singlets (1 Hz apart) together with the two methyleneamino signals. Thus the olefinic Me and methyleneamino signals of the free base isomers in $CDCl_3$ appear to be fortuitously identical to give this spectrum the appearance of a pure compound. It therefore seemed probable that the oxalate sample was a 50:50 mixture of both isomers (117 and 118). Conclusive proof of this postulate was obtained by use of the ASIS (Aromatic Solvent Induced Shifts) effect (Laszlo 1967 and references there cited). Thus, a spectrum of the free base in benzene separated the Me singlets by 6 Hz although the separation of the methyleneamino signals was reduced to 6 Hz. The distinct alteration of the olefinic Me shifts effects by this method is due to the differential solute:solvent collision complex structures for the two isomers in the magnetic field. The different anisotropic shielding effect by the

benzene solvent then caused the changes in resonance absorptions of the solutes.

The 50:50 mixed oxalate sample was submitted for pharmacological test together with the other 2-Me compounds.

(v) PHARMACOLOGICAL RESULTS AND DISCUSSION OF 3-AMINO-1
(2-PYRIDYL)PROP-1-ENES CONTAINING METHYL GROUPS

The pharmacological results obtained are given in Table XVII; generally speaking the activities of all these compounds were very low. The most active isomer was the o-tolyl trans (2-pyridyl/CH₂N)prop-1-ene (107) which still showed a figure of 40% inhibition after fifteen minutes when a 0.10 µg/ml. solution concentration was used. The potency of this compound, however, dropped markedly when the solution above was diluted tenfold. The related cis isomer (108) present in a 50:50 mixture of both compounds, appeared to be less active. It therefore appeared that the geometry of the o-tolyl trans isomer was quite favourable for blockade of the histamine receptors; most significantly this isomer was the only compound of all the Me derivatives tested which could have its cis aromatic/H (or Me) and dimethyleminomethyl functions predominantly in the same molecular plane (cf. the cis (H/Ph) aminobut-2-enes, the most active of the aminobutene isomers discussed in Chapter 3).

TABLE XVII

INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM BY SOME ISOMERS
AND MIXTURES OF METHYL CONTAINING 3-AMINO-1-ARYL(2-PYRIDYL)PROP-1-ENES

Sample	Compound(s) Number(s) in text	Conc. $\mu\text{g/ml}$	Percentage inhibition at time (in min.)									
			3	6	9	12	15	18	21	24	27	
trans(2-pyridyl/CH ₂ N)-3-dimethyl- amino-1(2-pyridyl)-1(o-tolyl)prop- 1-ene oxalate	(107) "	0.10 0.01	100 63	85 31	65 13	50 0	40 -	25 -	15 -	15 -	0 -	
50:50 mixture of above trans com- pound with its <u>cis</u> isomer as di- hydrobromides	(107)(108)	1.0	100	90	56	27	27	8	0	-	-	
Mepyramine standard	(37)	0.001	94	77	47	31	15	0	-	-	-	
"	"	"	100	95	73	57	0	-	-	-	-	
"	"	"	50	29	18	0	-	-	-	-	-	
"	"	"	69	52	38	10	0	-	-	-	-	
cis(2-pyridyl/CH ₂ N)-3-dimethylamino -2-methyl-1(2-pyridyl)-1-phenyl- prop-1-ene oxalate	(114)	0.10	33	24	14	5	-	-	-	-	-	
Mixture of above <u>cis</u> compound (30%) together with the <u>trans</u> isomer (70%) as oxalates	(113)(114)	0.10	19	19	10	19	19	10	10	0	-	
Mepyramine standard	(37)	0.001	49	36	27	25	19	15	-	-	-	
"	"	"	50	31	28	3	6	0	-	-	-	
"	"	"	62	46	24	19	13	0	-	-	-	

Continued

TABLE XVII (Continued)

Sample	Compound(s) Number(s) in text	Conc. µg/ml	Percentage inhibition at time (in min.)										
			3	6	9	12	12	15	18	21	24	27	27
Mixture of 2-methyl-1-phenyl-1 (2-pyridyl)-3-(1-pyrrolidino) prop-1-ene oxalates (85% <u>cis</u> : 15% <u>trans</u>)	(115) (116)	1.0	48	8	4	-	-	-	-	-	-	-	-
50:50 mixture of <u>cis</u> and <u>trans</u> 2-methyl-3-(1-piperidino)1-phenyl -1(2-pyridyl)prop-1-ene oxalates	(117) (118)	1.0	32	0	-	-	-	-	-	-	-	-	-
Mepyramine standard	(37)	0.001	100	96	76	57	38	27	13	13	-	-	-
"	"	"	100	53	16	15	13	-	-	-	-	-	-
"	"	"	60	45	23	27	13	-	-	-	-	-	-

N.B. In this table, a dash denotes discontinuation of experimental observation.

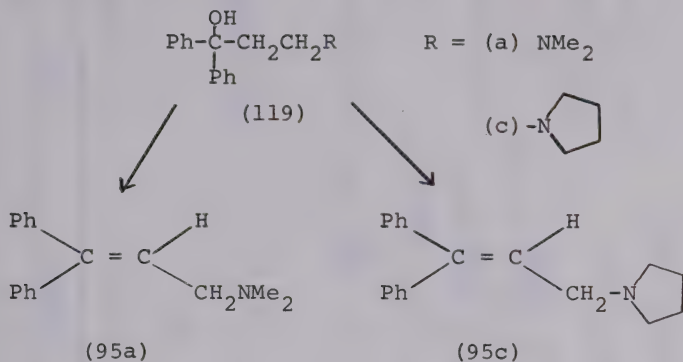
The 2-methyl compounds existed in isomeric mixtures in three out of the four samples (see Table XVII) tested but in each case extremely low antihistaminic potency was recorded; this suggested that the distinctly non-planar structures of these compounds were unsuited for effective interaction with the histamine receptors.

(vi) PREPARATION OF 1,1-DIARYLPROP-1-ENES

Adamson (1949) has previously prepared a series of 1,1-diphenylprop-1-enes (95) (see p. 114) which were shown to possess only moderate antihistaminic activities (Green et al. 1951). However, as our own results on 1-phenyl-1(2-pyridyl)prop-1-ene isomers did not conclusively indicate a stereospecific dependence upon activity it was decided to reprepare two typical examples of the 1,1-diphenyl series together with two Me derivatives for appropriate potency comparisons. In addition, preparation of the mono- and di-p-tolyl-3-pyrrolidinoprop-1-enes (125 and 127) was envisaged so that their activities could be compared to 'Triprolidine' (14). The latter potent antihistamine also contains the 3-pyrrolidino and 1-p-tolyl functions.

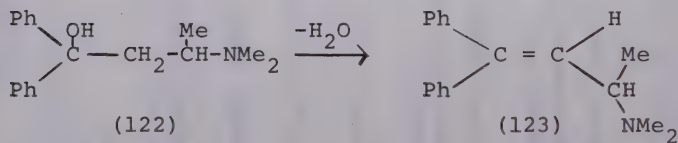
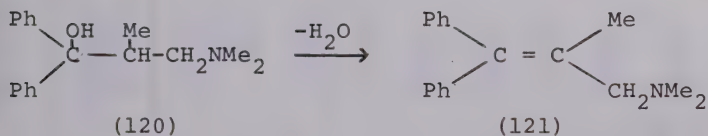
The two diphenylpropenes (95a and 95c) were the products of dehydration of the tertiary alcohols (119) which had been synthesized by reaction of phenyl-lithium with the appropriate Mannich ketones (Adamson 1949). The

PMR spectra of the two propenes were recorded for



reference purposes (see Table XVIII).

Preparation of the 2- and 3-Me prop-1-enes (121 and 123) was achieved by acid catalysed elimination of the appropriate carbinols (120 and 122) (Kjaer and Peterson 1951) using an acetic-hydrochloric acid mixture. The PMR spectrum of the 2-Me derivative (121)



SPECTRAL CHARACTERISTICS OF THE 1,2-DIARYLAMINOPROPENE ISOMERS

Sample	Compound Number in text	Chemical shifts ^a		λ_{\max} (ϵ) ^e
		Vinyl ^b -CH ₂ N	Others	
1,1-Diphenyl-3-dimethylamino-prop-1-ene.HCl	(95a)	389.5 (J7.5)	222 ^c NMe ₂ ^d 163(J5)	251 (13800)
Free base from above hydrochloride	(95a)	371 (J7)	178 ^d (J7) NMe ₂ ^f 132	-
1,1-Diphenyl-3(1-pyrrolidino)-prop-1-ene.HCl	(95c)	392 (J7)	226 ^c	252 (13800)
Free base from above hydrochloride	(95c)	377.5 (J6.5)	191.5 ^d (J6.5)	-
1,1-Diphenyl-2-methyl-3-dimethylaminoprop-1-ene.HCl	(121)	-	228 ^d (J5) =C-Me 131 ^f , NMe ₂ 163 ^d (J5)	227 (13300)
Free base from above hydrochloride	(121)	-	175 ^f =C-Me 110.5 ^f , NMe ₂ 127 ^f	-
1,1-Diphenyl-3-methyl-3-dimethylaminoprop-1-ene.HCl	(123)	376 (J10)	-	250 (12700)
Free base from above hydrochloride	(123)	368 (J10)	-C-H 232 ^g , NMe ₂ 162 ^c , Med 99.5 (J6.5) -C-H 177 ^h , NMe ₂ 133.5 ^f , Med 71.5 (J6.5)	-
50:50 mixture of cis and trans 1-phenyl-3(1-pyrrolidino)-1-p-tolylprop-1-ene.HCl's	(125)	387j (J7)	-k ArMe 143 ^f , 139 ^f	234 (14600) and 255 (13600)
Free base mixture from above	(125)	373j (J7)	191 ^d , 189 ^d (J7) ArMe 141.5 ^f , 138 ^f	-
1,1-di-p-tolyl-3(1-pyrrolidini)-prop-1-ene.HCl	(127)	387.5 (J7.5)	225 ^c ArMe 144 ^f , 139.5 ^f	237 (15500) and 257 (14400)
Free base from above hydrochloride	(127)	374 (J7)	196 ^d (J7) ArMe 143 ^f , 139 ^f	-

Continued

TABLE XVIII (Continued)

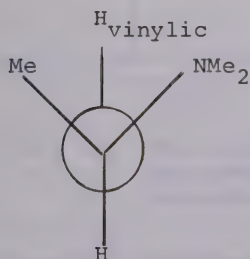
- a Chemical shifts in Hz from TMS (internal standard) at an operating frequency of 60 MHz; solvent CDCl_3 , coupling constants (J) in Hz.
- b Triplet.
- c Doublet of doublets (J's 7.5 and 5).
- d Doublet.
- e Solvent H_2O , λ_{max} is wavelength in $\text{m}\mu$; extinction coefficient (ϵ) shown in parenthesis.
- f Singlet.
- g Centre of octet.
- h Centre of quintet.
- j Superimposed triplets.
- k Masked by pyrrolidino bands.

was straightforward but that of the 3-Me compound (123) was more complex; several signals of the latter compound (given below and in Table XVIII) were of interest and will now be discussed.

Chemical shifts in Hz (from TMS)
CDCl₃ solution

<u>Form</u>	<u>Vinylic doublet</u>	<u>Methine multiplet</u>	<u>NMe₂</u>	<u>Me doublet</u>
123 (free base)	368 (J10 ^A)	177 (centre) ^B	133.5	17.5 (J6.5)
123 (.HCl)	376 (J10 ^A)	232 (centre) ^B	162 ^C	99.5 (J6.5)

A. Vinylic Signals. The exceptionally large coupling constant ($J = 10$) between the methine and vinylic hydrogen is probably explained by the existence of the preferred conformation shown by the Newman diagram in Figure 11.



Preferred conformation of compound (123) looking down the C₂-C₃ bond.

Figure 11.

This conformer allows an angle of 180° between the coupled vicinal protons which according to Karplus' (1959; 1963) relationship (describing the magnitude of vicinal proton-proton coupling as a function of the dihedral angle in the H-C-C-H bond system) should result in J_{vicinal} being of the order of 9-10 Hz.

B. Methine Signals. First order treatment of the methine proton (using the observed coupling constants of 10 and 6.5 Hz) predicts a multiplet with the relative line intensities and parameters shown in Figure 12. Actual examination of the expanded and amplified methine

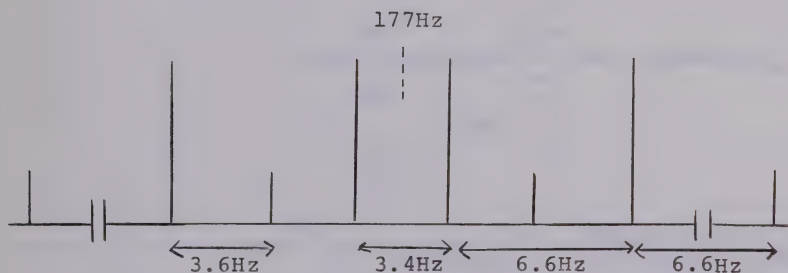
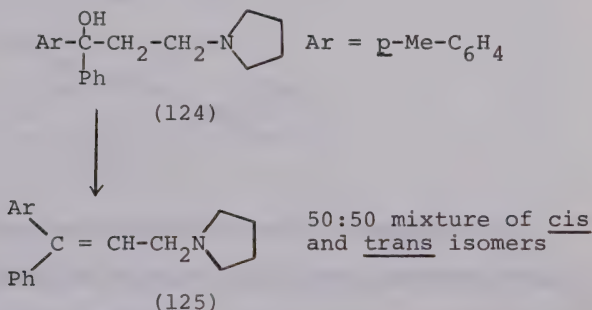


Figure 12. Theoretical and observed 60MHz line positions and intensities of the methine multiplet of compound (123) in the free base form.

signal of the free base revealed it to have precisely the same characteristics to those predicted. In the case of the hydrochloride salt, additional coupling (J_{NH}^+ type) broadens the lines of the multiplet so that overlap occurs and a quintet is observed.

C. Dimethylamino Signals. In the hydrochloride spectrum, the dimethylamino group is seen as an overlapping doublet of doublets. This observation is a direct result of the preferred conformation shown in Figure 11 which causes the two N-Me groups to be magnetically non-equivalent; coupling with the $\overset{+}{N}$ -H proton then produces the doublet of doublets. The whole phenomenon is only observed, however, because of the inversion rate of the Me groups on the $\overset{+}{N}$ -H centre presumably being slow on the NMR time scale.

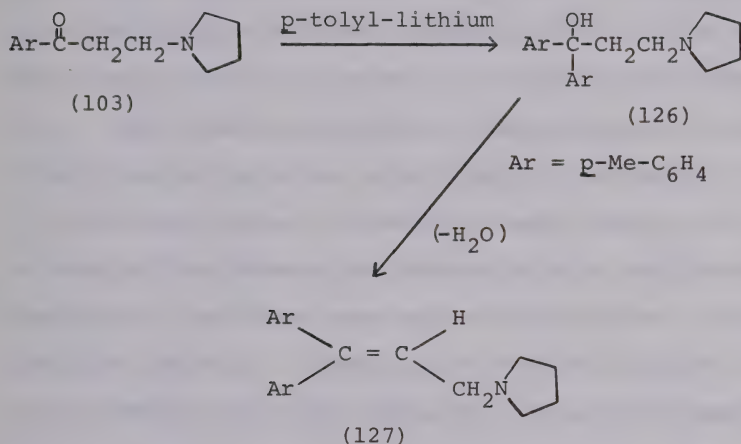
Synthesis of the mono p-tolyl carbinol (124) was realized by reaction of phenyl-lithium with the appropriate



Mannich base (103). Acid-catalysed elimination of the tertiary alcohol and fractional crystallisation of the hydrochloride mixture led to no dissociation of the original 50:50 mixture of the cis and trans aminopropenes (125) (shown by the duplication of the aryl-Me and methyleneamino signals in the PMR spectrum of the product). It therefore

appears that the physical properties of the two isomers are extremely similar.

The di-*p*-tolyl carbinol (126) was prepared by reaction of the appropriate *p*-tolyl Mannich base (103) with *p*-tolyl-lithium reagent. Dehydration of the tertiary alcohol then yielded the novel di-*p*-tolylaminopropene (127).



The PMR characteristics of this compound together with the previously discussed mixture (125) were unexceptional and are given in Table XVIII.

All the phenylpropene compounds described in this section were submitted for antihistaminic evaluation and the results so far obtained will now be discussed.

(vii) PHARMACOLOGICAL DISCUSSION AND RESULTS OF THE 1,1-DIARYL-AMINOPROPENES

The results received to date are given in Table XIX;

the three related diphenyl isomers (95a, 121 and 123) tested had either very low activities or were completely inactive as in the case of compound (121).

The 50:50 mixture of the cis and trans 1-phenyl-3 (1-pyrrolidino)-1-p-tolyl-prop-1-ene hydrochloride isomers (125) had significant activity as shown by the semi-quantitative results given in Table XIX. A subsequent pA_2 determination produced a figure of 8.5 for the mixture which was close to the value of 9.0 for 'Triprolidine' (14). The isomers contained in the mixture only differ from Triprolidine by the substitution of a phenyl ring for the 2-pyridyl group; it therefore seems likely that either or both of the isomers is interacting with the histamine receptors in much the same way as Triprolidine to produce the high activity. A decision on whether only one or both of the isomers are responsible for the activity may yet be reached when data on the di-p-tolyl compound (127) is available (separation of the isomers for individual testing appears extremely difficult owing to the very close physical properties of the two compounds, see p. 151). If the di-p-tolyl isomer (127) is largely inactive this would suggest that the cis (Ph/H) isomer of structure (125) (with its p-tolyl group out of the plane of the double bond) is stereospecifically active assuming that the antagonists have related modes of action. Conversely, if the compound (127) has very potent antihistaminic activity then the cis

TABLE XIX

INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM BY SOME

3-AMINO-1,1-DIARYLPROP-1-ENES

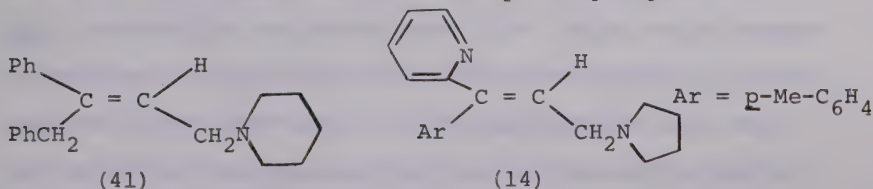
Sample	Compound(s) Number (s) text	Conc. μg/ml	Percentage inhibition at time (in min.)														
			3	6	9	12	15	18	21	24	27						
1,1-Diphenyl-3-dimethylaminoprop-1-ene.HCl	(95a)	0.10	60	40	15	0	-	-	-	-	-						
1,1-Diphenyl-2-methyl-3-dimethylaminoprop-1-ene.HCl	(121)	0.10	0	-	-	-	-	-	-	-	-						
1,1-Diphenyl-3-methyl-3-dimethylaminoprop-1-ene.HCl	(123)	0.10	32	25	17	-	-	-	-	-	-						
Mepyramine standard	(37)	0.001	49	36	27	25	19	15	-	-	-						
"	"	"	50	31	28	3	6	0	-	-	-						
"	"	"	62	46	24	19	13	0	-	-	-						
50:50 mixture of cis and trans 1-phenyl-3(1-pyrrolidino)-1-p-tolylprop-1-ene.HCl's	(125)	1.0	100	100	100	100	-	-	-	-	-						
"	"	0.01	39	21	11	14	7	-	-	-	-						
Mepyramine standard	(37)	0.001	50	32	22	15	10	9	4	-	-						
"	"	"	66	33	23	9	4	-	-	-	-						

N.B. In this table, a dash denotes discontinuation of experimental observation.

(p-tolyl/H) isomer of (125) should be the active compound responsible for the high activity of the mixture (125).

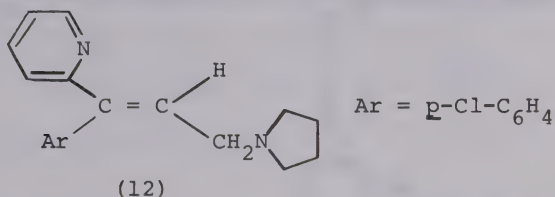
(viii) ATTEMPTS TO INTRODUCE THE 2-PYRIDYL HETEROCYCLE INTO AN AMINOBUTENIC STRUCTURE

So far the most potent antihistaminic compounds discovered during the course of this work are the cis (H/Ph) 1,2-diarylaminobut-2-enes (58) which were discussed in Chapter 3; the key to their activity is considered to be the coplanar 2-phenyl-vinylic methyleneamino features of their structures which appear to allow marked interaction and blockade of the histamine receptors (see p. 111). The most active member of the cis (H/Ph) aminobut-2-enes is the piperidino derivative (41) which has a pA_2 value of 8.76; however, the magnitude of this pharmacological parameter is still less than the corresponding figure of 9.0



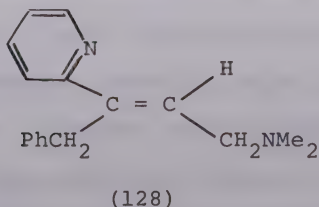
for Triprolidine (14). As the latter antihistamine may also adopt a similar conformation to this cis (H/Ph) aminobut-2-enes (58) (with the 2-pyridyl ring in the same molecular plane as the vinylic and methyleneamino functions) the question arises of the necessity or importance of the 2-pyridyl function for high activity.

Adamson (1951) and Green (1953b) have already shown that the trans (2-pyridyl/CH₂N) p-chlorophenyl compound (12) and Triprolidine (14) itself are considerably more active than their corresponding cis (2-pyridyl/CH₂N) isomers; such evidence suggests that it may be an advantage to have a coplanar 2-pyridyl rather than a substituted phenyl function present in aminopropenes to produce

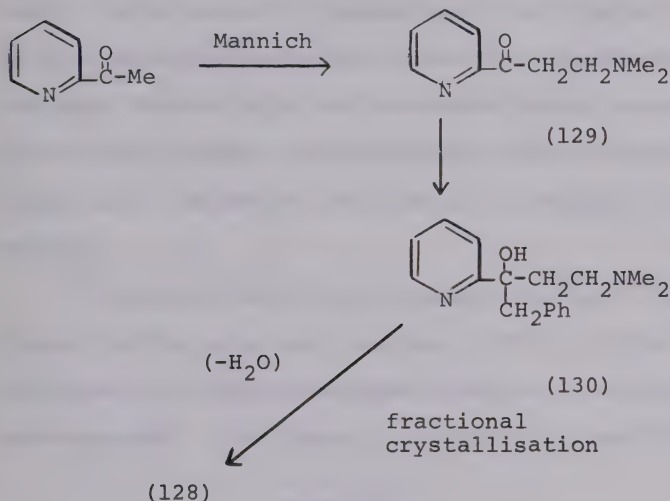


potent antihistaminic compounds. This observation is in line with the common appearance of the 2-pyridyl group in clinically used antihistamines e.g. Pyribenzamine (96).

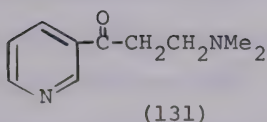
Accordingly, attempts were made to synthesize the cis (2-pyridyl/H) aminobut-2-ene (128) which would contain a coplanar 2-pyridyl function within the active cis (H/Ar) aminobut-2-ene structure. It was anticipated that this new molecule would possess high antihistaminic activity.



The first synthetic route envisaged for preparation of the required aminobut-2-ene (128) is shown below; the 2-pyridyl Mannich base (129) has been mentioned only once in the literature (DeStevens 1963) but no experimental details were given. Unfortunately, our own

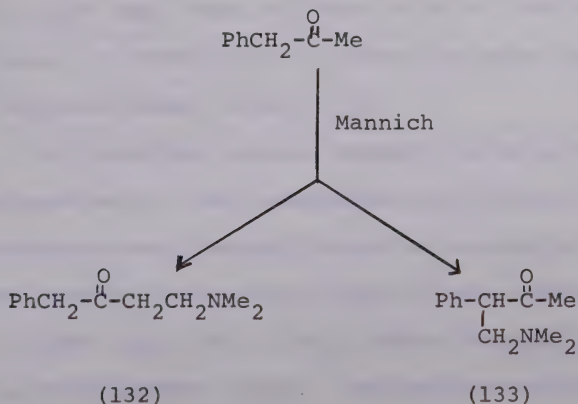


Mannich reaction failed with an intractable black solution being formed when the reactants were heated under reflux (either with or without the employ of an atmosphere of N_2). Myers (1963) similarly failed to isolate any product from a Mannich reaction using 2-propionyl pyridine as the substrate. A sample of the related 3-pyridyl Mannich ketone (131) was prepared, however, in low yield (35%) after modifying the literature method of McElvain and Snell (1934); it was found necessary to use an adequate



excess of hydrochloric acid for this reaction to proceed. Unfortunately, treatment of the 3-pyridyl base (131) with benzylmagnesium chloride (in both ether and toluene) yielded only the unchanged ketone precursor; thus, the 3-pyridyl function could not be introduced into a cis (H/Ar) aminobut-2-ene as an alternative pyridyl moiety.

Attention was then focused onto other possible routes to the precursor carbinol (130); in this context, the reaction of phenylacetone under Mannich conditions was investigated. Two ketonic products (132 and 133) are



possible from this reaction and if the benzylic ketone (132) could be isolated, its treatment with 2-pyridyl-lithium would yield the required carbinol (130).

The amounts of each Mannich product will be controlled by the relative labilities of the methylenic or methyl α -hydrogen atoms present in the substrate. On this basis, the methyl ketone (133) should be the preferred product as the methylenic protons will be the more reactive α -hydrogens of phenylacetone, being doubly activated by the inductive influences of both the phenyl and carbonyl groups. A paper by Kyi and Wilson (1952) supports this contention as these authors actually obtained the methyl ketone (133) (which gave a positive iodoform test) after Mannich reaction of phenylacetone. However, a later reference (Patent, 1953b) by the Sharp and Dohme Company concerning the same reaction under similar conditions was completely contradictory in reporting sole formation of the required benzyl ketone (132).

We therefore reinvestigated the Mannich reaction of phenylacetone so that examination of the product by PMR spectroscopy would establish the true course of the reaction. A pure crystalline hydrochloride of the product was obtained and its PMR spectrum in CDCl_3 proved the exclusive formation of the methylketone (133). The PMR characteristics of this compound are given below and several interesting signals will now be discussed:

Chemical shifts in Hz
from TMS; CDCl₃ solution

	<u>C-H</u>	<u>-CH₂N</u>	<u>NMe₂</u>	<u>$\overset{\text{O}}{\parallel}$ C-Me</u>
Compound (133) .HCl	288 ^a	244 ^b , 187 ^c	167.5 ^d	130 ^e

^a doublet of doublets, J_{AX} 4.5 and J_{MX} 7.5 Hz

^b (H_B) octet, J_{AM} 13, J_{MX} 7.5 and J_{NH^+} 5 Hz

^c centre of (H_A) quintet, J_{AM} 13, J_{AX} 4.5 and J_{NH^+} 5 Hz

^d doublet of doublets, J's 7 and 5 (NH^+)

^e singlet

Methyleneamino Signals. These signals appear as a low field octet and a higher field quintet whose separation is 57 Hz. Methylene protons directly linked to an asymmetric carbon atom (as in this example) are intrinsically non-equivalent but the observation of pronounced chemical shift differences usually indicates the existence of a preferred conformation (Hall and van Gorkom 1968). The favoured rotamer most suited to interpretation of the results is shown in Figure 13, with the methylene protons

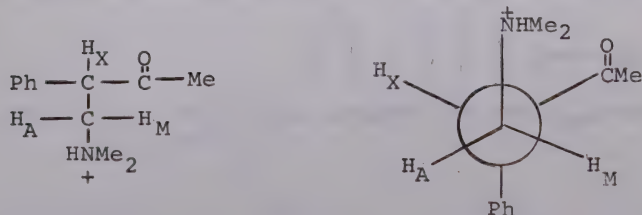


Figure 13. The postulated preferred conformer of the AMX methyl ketone (133).

(H_A and H_M) forming part of an AMX spin-system with the methine proton (H_X). Within the preferred conformation, H_M will form the lower field multiplet due to the combined deshielding influences of the adjacent carbonyl and phenyl groups. The appearance of the H_M multiplet as an octet is explained by the splitting pattern shown in Figure 14 using the appropriate three coupling constants J_{AM} (13 Hz), J_{MX} (7.5 Hz) and J_{NH}^+ (5 Hz) (the higher value of J_{MX} (7.5 Hz) compared to J_{AX} (4.5 Hz) is explained by the respective vicinal dihedral angles of 180° and 60° and the $\cos^2\phi/3J$ relationship of Karplus).

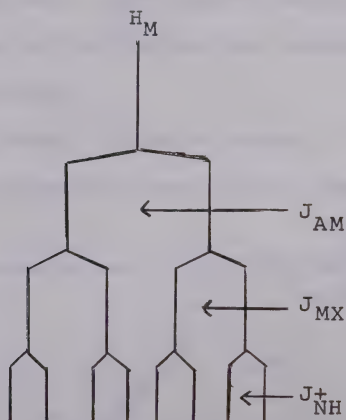


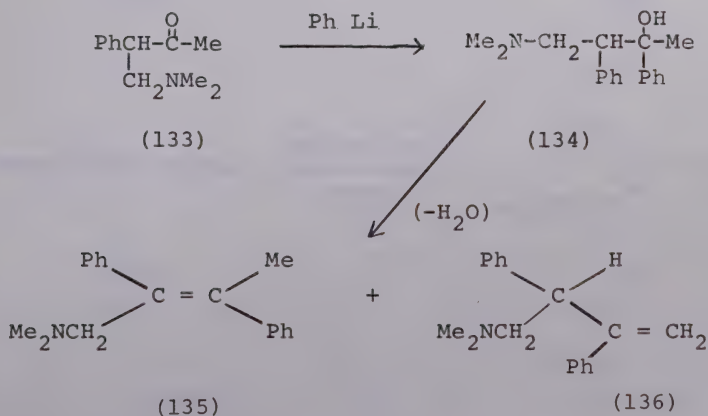
Figure 14. Splitting pattern for the H_M proton of compound (133).

Similarly, the H_A multiplet arises from splitting by J_{AM} , J_{AX} (only 4.5 Hz) and J_{NH}^+ ; some overlap occurs during the final splitting so that only a quintet is actually observed.

Methine Signals. This signal is observed as a doublet of doublets as the methine proton is coupled to each of the non-equivalent methylene hydrogens.

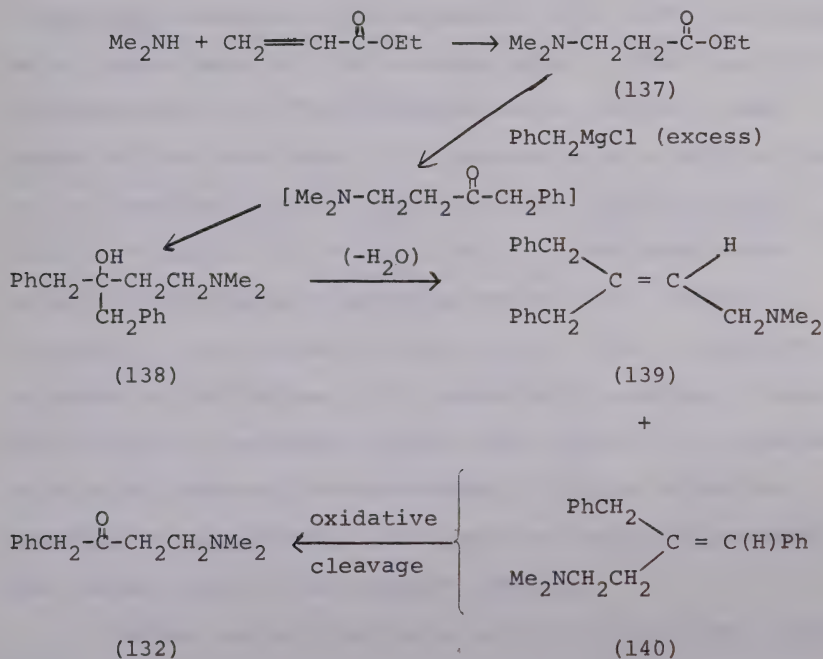
Dimethylamino Signals. The dimethylamino group becomes magnetically non-equivalent as a result of the preferred conformation depicted in Figure 13; coupling between each N-Me group (the inversion rate of the Me groups on the N^+ -H centre presumably being 'NMR slow') together with further signal splitting by the N^+ -H proton produces the observed doublet of doublets.

Although the 'wrong' ketonic product (133) had now been obtained from the Mannich reaction of phenylacetone



the former was nevertheless treated with phenyl-lithium and the resulting carbinol (134) dehydrated to afford two new aminoalkenes (135 and 136). These two products were identified by their PMR characteristics (see experimental) but subsequent testing for antihistaminic potency revealed that both compounds had negligible activities.

After the failure of the second Mannich route, a final attempt to obtain the required benzyl ketone (132) was pursued according to the following scheme:



The first step of the synthetic pathway involved condensation of dimethylamine with ethyl acrylate to afford the dimethylamino ethyl propionate (137). Treatment of the latter with excess benzylmagnesium chloride yielded the dibenzyl carbinol (138) possibly after transient formation of (132). The penultimate stage of the sequence then consisted of dehydration (under acid-catalysed conditions) of the carbinol product (138) which yielded a mixture of the dibenzyl aminobut-2-ene (139) and a cis/trans mixture of the aminobut-1-enes (140) in approximately equal amounts (PMR integral data). Fractional crystallisation of the hydrochloride salts yielded a pure sample of the but-2-ene (139) together with a 50:50 mixture of the required cis and trans but-1-ene hydrochlorides (140). Finally, the latter mixed but-1-ene sample was treated with potassium permanganate solution at 0-10° according to the method of Frey et al. (1950); oxidative cleavage to the ketone (132) undoubtedly occurred (a black precipitate of manganese dioxide and the smell of benzaldehyde being observed) but unfortunately further oxidation, probably to phenylacetic acid, aborted use of this method for preparation of the required compound.

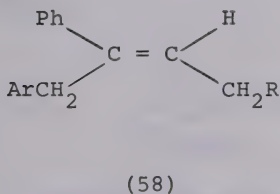
Future use of this route to obtain the benzyl ketone (132) might be successful if a milder oxidative cleavage reaction such as ozonolysis or use of the osmium tetroxide-iodate reagent were employed. However, our own efforts were terminated at this point.

CHAPTER 5

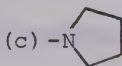
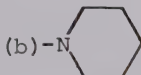
APPLICATION OF THE PRINCIPLE OF THE ADDITIVITY OF SHIELDING
EFFECTS IN OLEFINIC COMPOUNDS FOR CONFIGURATIONAL ASSIGNMENTS
IN 4-AMINO BUT-2-ENES

APPLICATION OF THE PRINCIPLE OF THE ADDITIVITY OF SHIELD-
ING EFFECTS IN OLEFINIC COMPOUNDS FOR CONFIGURATIONAL
ASSIGNMENTS IN 4-AMINOBUT-2-ENES

The cis (H/Ph) 4-aminobut-2-enes (58) have proved to be the most active of all the novel antihistamine compounds described in this thesis. The configurations of these isomers were assessed by comparison of their PMR characteristics with related trans (H/Ph) but-2-ene isomers; consideration of the differential shielding



R = (a) NMe₂



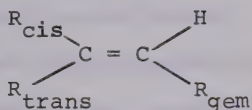
effects of the various groups present in these molecules then led to appropriate assignments (see Chapter 3).

However, it was considered desirable to verify the assignments by an alternative PMR approach. To this end, application of the principle in the additivity of shielding effects in olefinic compounds was investigated. This phenomenon is now well documented (Tobey 1969, and references there cited) and an international group (Meier et al. 1966; Matter et al. 1969) initially established a method

for configurational assignments based on the independence and additivity of vinyl substituent shielding effects. These authors computed a large number of vinylic shifts (in CDCl_3 or CCl_4 solution) derived from the literature and established the following expression for the chemical shift (δ) of any olefinic proton:

$$\delta = \text{base value} + \sum_i Z_i$$

where Z_i are the respective shielding increments for substituents (R) in the gem, cis and trans relationships to the proton.



The shielding increments for hydrogen were taken as zero and the base value used was the calculated value for ethylene (5.25 ppm). A statistical treatment of the chemical shift data obtained from the numerous olefinic compounds afforded a number of substituent constants (Z_{gem} , Z_{cis} and Z_{trans}). These characteristic 'Z' values for various groups could be substituted into the expression given below to predict the chemical shift (in ppm) of an

$$\delta_{\text{C}=\text{C}-\text{H}} = 5.25 + Z_{\text{gem}} + Z_{\text{cis}} + Z_{\text{trans}}$$

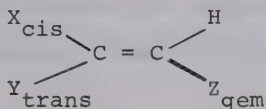
olefinic proton ($\delta_{\text{C}=\text{H}}$) from internal TMS. Thus, the method could be applied to configurational problems in cis and trans olefinic isomers. Differentiation of the isomers could be achieved by comparison of predicted and observed olefinic chemical shift values in suitable examples.

However, a number of conspicuous exceptions from the calculated values were noted by the group; these were attributed primarily to conjugative interactions between substituents. An attempt to take this into account was made by listing two sets of Z values for carbonyl and other unsaturated substituents. One set was used when such substituents were present alone on the double bond ('solo' Z values). The other was used when two or more groups capable of conjugation were present together ('conj.' Z values).

Tobey (1969) criticized this approach as an oversimplification of the whole problem; he postulated that the co-operative shielding effects of two substituents capable of conjugative interaction depended markedly on the relative geometries of the two groups. He also speculated that significant dipole-dipole and steric interactions (in addition to conjugate interactions) were frequently operating between highly polar, anisotropic substituents. Tobey established his own series of mean substituent constants (σ values) which he derived from

a relatively small number of appropriately substituted ethylenes as solutes in CDCl_3 or CCl_4 . Moreover, the σ values were obtained only from olefins containing small and symmetrical functional groups; in this way, it was hoped to minimise the erratic shielding effects produced by the various substituent interactions. Nevertheless, Tobey's constants agreed closely with the Z values cited by Matter and Meier's group.

Furthermore, the equation quoted by Tobey (see below) for the prediction of the resonance position of a vinylic proton was necessarily of much the same form as



$$\delta_{\text{C}=\text{C}-\text{H}} \text{ (ppm)} = -5.27 + \sigma_{\text{cis-X}} + \sigma_{\text{trans-Y}} + \sigma_{\text{gem-Z}}$$

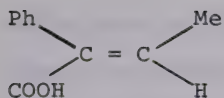
that previously proposed by the international group.

However, he also postulated a 'model compound' approach for prediction of the resonance positions of vinylic protons within trisubstituted ethylenes bearing two interacting substituents. In such cases, use of Z or σ 'constants' for configurational assignments is often misleading, especially if one or both of the interacting groups are anisotropic. This is because the average orientation and effective shielding influences of two interacting groups depend upon the complexity of

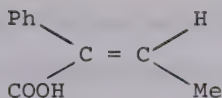
their interactions which, in turn, is controlled by the relative dispositions of these groups within the molecule.

Tobey's solution to this problem was to choose a disubstituted olefinic compound or compounds from the literature which contain(s) the interacting substituents in appropriate, unambiguous molecular environments. The model compound was then 'converted' into the desired trisubstituted ethylene by application of the appropriate σ value for the third substituent (ideally, small and symmetrical). This procedure thus automatically accounted for any major aberrations from the normal shielding effects of the two interacting substituents.

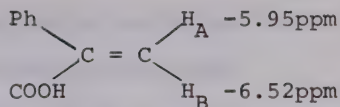
As an example of this approach Tobey cited the unambiguous assignment of configurations to the cis (Ph/Me) and trans (Ph/Me) β -methylatropic acids (141 and 142) using atropic acid (143) as the model compound. The chemical shifts of protons H_A and H_B in atropic acid are -5.95 and -6.52 ppm respectively and the observed vinylic resonance positions of the two β -methylatropic acids (of unassigned configurations) are -6.40 and -7.0 ppm. Conversion of the model compound (143) to the cis (Ph/Me) isomer (141) by appropriate application of $\sigma_{\text{gem Me}}$ (-0.44 ppm) affords a predicted vinylic shift of $-6.52 + (-0.44)$



(141)



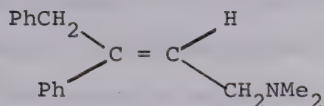
(142)



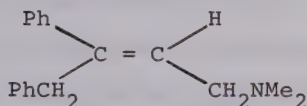
(143)

= 6.96 ppm. Similarly, the theoretical value for the vinylic proton of the trans (Ph/Me) isomer (142) is $-5.95 + (-0.44) = -6.39$ ppm. Hence the predicted values for the cis (-6.96 ppm) and trans (-6.39 ppm) isomers agree very closely with the observed values of -7.0 and -6.40 ppm which leads to appropriate configurational assignments to the two β -methylatropic acids (141 and 142).

In our own work we wished to check the configurations of a pair of cis and trans (H/Ph) aminobut-2-enes using the additivity principle. The dimethylamino isomers (32 and 33) were considered the most suitable compounds



(32)



(33)

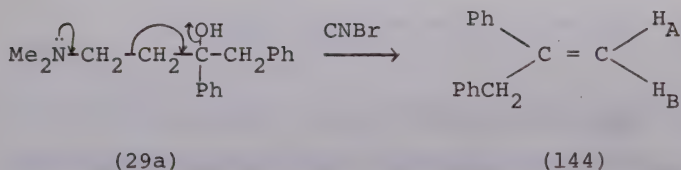
as they contained the smallest basic group in our series; thus, the overall steric interactions would be minimised in these two isomers which would enhance the possibility of successful application of the additivity principle.

It was decided to obtain our own σ values for the benzyl and protonated dimethylamino groups (in CDCl_3)

as no precise σ or Z values were available for either of these two moieties (Matter and his group, 1969, have only published Z values for the CH_2NR_2 and $\text{CH}_2\text{-Aryl}$ functions using data from variously substituted groups of these types). Then, having obtained the required σ values the predicted vinylic shifts of the cis and trans isomers (32 and 33) could be calculated by two methods:

1. Straightforward substitution of the appropriate σ_{gem} , σ_{cis} and σ_{trans} values into Tobey's equation.
2. The single model compound approach of Tobey (1969) using 2,3-diphenylprop-1-ene (144) as the reference structure.

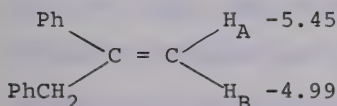
The model prop-1-ene (144) also served as an appropriate compound from which to obtain cis and trans σ values for the benzyl function positioned geminal to a phenyl ring. The former compound was prepared by fragmentation of 4-dimethylamino-1,2-diphenylbutan-2-ol (29a) with cyanogen bromide (the probable mechanism is shown below); the latter



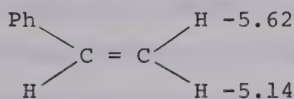
reagent has previously been shown to induce the fragmentation of 4-dimethylamino-3-methyl-1,2-diphenylbutan-2-ol and related γ -hydroxy acyclic tertiary amines (Casy et al., 1969). The 60 MHz spectrum of the distilled product (in CDCl_3)

provided the required shifts (from TMS) of the H_A (327 Hz or -5.45 ppm) and H_B protons (300 Hz or -4.99 ppm) (see structure 144); it was reasonably assumed that H_A will be the lower field vinylic proton because of its cis relationship to the strongly deshielding phenyl group.

The H_A and H_B vinylic characteristics agreed precisely with the values calculated from the reported 100 MHz data on the same compound (Bumgardner 1966). Comparison of the H_A and H_B vinylic shifts (in ppm) of the model



(144)



(102)

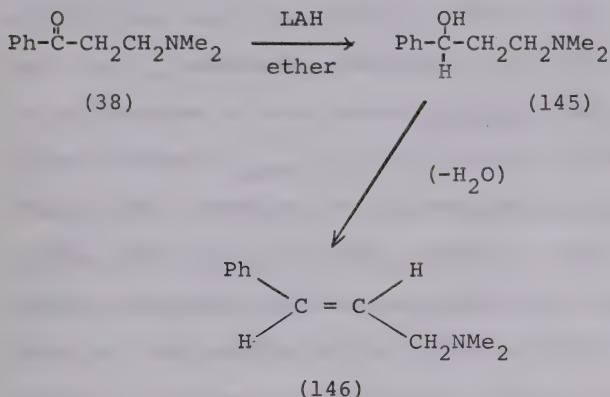
prop-1-ene (144) with the appropriate absorptions quoted (Tobey 1969) for styrene (102) gave:

$$\sigma_{\text{trans PhCH}_2} = -5.45 - (-5.62) = \underline{+0.17}$$

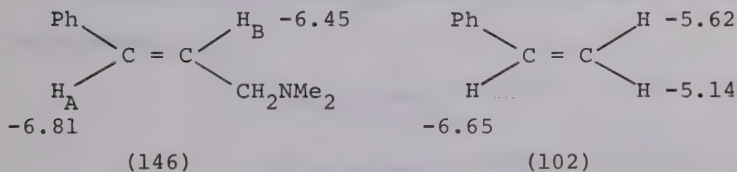
$$\sigma_{\text{cis PhCH}_2} = -4.99 - (-5.14) = \underline{+0.15}$$

In a similar fashion the cis and gem σ values for the protonated dimethylaminomethyl function were calculated by comparison of the appropriate vinylic shifts of styrene and trans 3-dimethylamino-1-phenylprop-1-ene (146). The latter compound was synthesized as shown

below with the secondary alcohol (145) being dehydrated



with the usual acetic-hydrochloric acid mixture. The styrenoid UV spectrum (λ_{max} 252 m μ , ϵ 19,000) of the product confirmed its speculated trans configuration (Holmes and King 1947). The PMR spectrum of the trans



propene (146) as a solute in CDCl_3 at 60 MHz revealed seven peaks in the vinylic region. A repeat spectrum in the same solvent at 100 MHz was simplified by irradiation of the CH_2N signal which allowed the H_A and H_B protons to appear as an AB quartet. Analysis of the latter spin system using Bible's technique (1965) led to chemical shift values in Hz for H_A and H_B at 100 MHz.

Simple conversion to 60 MHz values then gave $H_A = 408.6$ Hz or -6.81 ppm and $H_B = 387$ Hz or -6.45 ppm. It was assumed that the H_A resonance absorption was lower field than that for H_B because of the greater geminal deshielding effect on the former ($\sigma_{\text{gemPh}} = -1.43$ ppm) by the phenyl group (Tobey 1969) compared to the combined cis phenyl and gem $\text{CH}_2^+\text{NMe}_2$ influences on the H_B proton. This fact was confirmed during the decoupling experiment; the low field H_A 'doublet' was unaffected by the irradiation of the CH_2N signal in contrast to the higher field H_B signal (5 peaks) which collapsed to form the other half of the AB quartet. Only the H_B vinylic proton is in a position to be coupled to the CH_2N protons which thus proved the positional assignments of H_A and H_B within compound (146).

Using the H_A and H_B data the following σ values were calculated:

$$\sigma_{\text{gem CH}_2^+\text{NMe}_2} = -6.45 - (-5.62) = \underline{-0.83}$$

$$\sigma_{\text{cis CH}_2^+\text{NMe}_2} = -6.81 - (-6.65) = \underline{-0.16}$$

Hence, we were now in a position to apply the additivity principle to the cis and trans dimethylaminobut-2-enes (32 and 33).

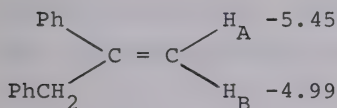
Initially the predicted vinylic shift value for the cis (H/Ph) isomer (33) was calculated directly from Tobey's equation:

$$\delta_{\text{C}=\text{C}-\text{H}}(33) = -5.27 + \sigma_{\text{cis Ph}} + \sigma_{\text{trans PhCH}_2} + \sigma_{\text{gem CH}_2^+\text{NMe}_2}$$

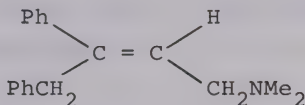
(Tobey, 1969, gives $\sigma_{\text{cis Ph}} = -0.39$)

$$\therefore \delta_{\text{C}=\text{C}-\text{H}}(33) = -5.27 + (-0.39) + (+0.17) + (-0.83) = \underline{-6.32}$$

Tobey's 'model compound' approach was then employed for a second evaluation of the vinylic resonance; this involved addition of $\sigma_{\text{gem CH}_2^+\text{NMe}_2}$ to the appropriate H_A vinylic shift of the model compound (144) to 'convert' the



(144)



(33)

latter into the cis (H/Ph) isomer (33):

$$\text{Thus, } \delta_{\text{C}=\text{C}-\text{H}}(33) = -5.45 + \sigma_{\text{gem CH}_2^+\text{NMe}_2}$$

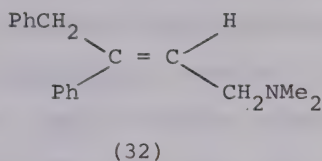
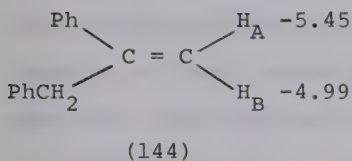
$$= -5.45 + (-0.83)$$

$$= \underline{-6.28}$$

Hence, the predicted values of -6.32 and -6.28 ppm from the two additivity methods agreed very well with the observed value of -6.30 ppm for the postulated cis (H/Ph) isomer. In contrast, the observed figure (-5.97 ppm) for the proposed trans (H/Ph) isomer (32) diverged markedly from the calculated value for the cis isomer; therefore,

the PMR additivity principle gave strong support to our original configurational assignment to the cis compound.

In the same fashion the predicted vinylic shift value for the trans (H/Ph) isomer (32) was determined



by the two methods. Direct substitution of the appropriate σ values in Tobey's equation gave:

$$\begin{aligned}
 \delta_{\text{C}=\text{H}}^{(32)} &= -5.27 + \sigma_{\text{cis PhCH}_2} + \sigma_{\text{trans Ph}} + \sigma_{\text{gem CH}_2^+\text{NMe}_2} \\
 &\quad (\text{Tobey, 1969, gives } \sigma_{\text{trans Ph}} = +0.06) \\
 &= 5.27 + (+0.15) + (+0.06) + (-0.83) \\
 &= \underline{-5.89}
 \end{aligned}$$

Use of the model compound method gave:

$$\begin{aligned}
 \delta_{\text{C}=\text{H}}^{(32)} &= -4.99 + (-0.83) \\
 &= \underline{-5.82}
 \end{aligned}$$

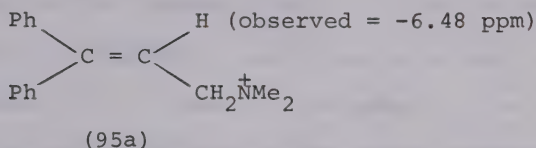
Thus the predicted values were in fair agreement with the observed shift of -5.97 ppm for the trans isomer. The somewhat low figure of the predicted vinylic shift derived from the model compound approach is probably attributable

to the undoubted steric interactions between the adjacent phenyl and methyleneamino groups (Casy and Pocha 1967). Such steric clashing must invalidate use of the $\sigma_{\text{gem}} \text{CH}_2^+ \text{NMe}_2$ value for 'conversion' of the model compound to the trans isomer because this figure represents the shielding effect of the protonated methyleneamino group in a freely rotating, unhindered situation. In addition, the orientation and trans shielding effect of the phenyl ring in the trans isomer (32) will also be affected.

The superior agreement of the predicted vinylic shift derived by the direct substitution method is presumably due to a cancellation of any errors derived from the particular σ 'constants' used. Indeed, Tobey (1969) has commented that uncertainties in σ values tend to compensate rather than propagate when used additively. He also noted that the 'model compound' approach is most fruitful when the σ value for a small and non-interacting substituent (unlike the $\text{CH}_2^+ \text{NMe}_2$ group in our example) is used to 'transform' a disubstituted model structure into the desired trisubstituted ethylene.

Moreover, it was found that the predicted vinylic shift for the trans isomer (32) could be refined to a value closer to the observed figure of -5.97 ppm. This was achieved by obtaining a $\sigma_{\text{trans Ph perturbed}}$ value from

the diphenyl reference compound (95a) (preparation, p. 146) to replace the unperturbed $\sigma_{\text{trans Ph}}$ figure originally used; the phenyl dimethylaminomethyl interaction in the latter compound was considered to be very similar to that contained in the trans (H/Ph) but-2-ene as both compounds contained the interacting groups in



juxtaposition. Appropriate substitution in Tobey's equation yielded

$$\begin{aligned}
 \delta_{\text{C}=\text{C}-\text{H}}(95\text{a}) &= -6.48 = -5.27 + \sigma_{\text{cis Ph}} + \sigma_{\text{gem CH}_2\text{NMe}_2^+} \\
 &\quad + \sigma_{\text{trans Ph perturbed}}
 \end{aligned}$$

$$\text{But } \sigma_{\text{cis Ph}} = -0.39 \text{ (Tobey 1969)}$$

$$\sigma_{\text{gem CH}_2\text{NMe}_2^+} = -0.83 \text{ (see p. 175)}$$

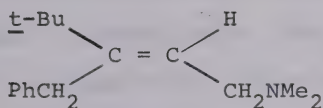
$$\begin{aligned}
 \therefore \sigma_{\text{trans Ph perturbed}} &= -6.48 + 0.39 + 5.27 + 0.83 \\
 &= \underline{+0.01}
 \end{aligned}$$

Substitution of the perturbed phenyl value into Tobey's equation (instead of $\sigma_{\text{trans Ph}} = +0.06$) afforded a predicted vinylic shift of -5.94 ppm which was in excellent agreement with the observed value of -5.97 ppm for

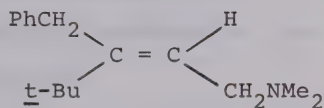
the trans isomer.

Thus, application of the additivity principle to the cis and trans aminobut-2-ene compounds (32 and 33) provided strong corroborative evidence for the original configurational designations to the two isomers which had been based on consideration of the differential shielding effects of the various groups present in these molecules.

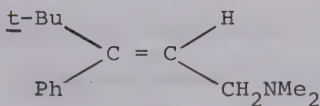
It was also decided to apply the principle to the t-Bu aminoalkenes (76, 79 and 86) discussed at the end of Chapter 3. The configurations of the benzyl compounds



(76)



(79)



(86)

(76 and 79) have already been assigned using arguments based on a qualitative assessment of differential shielding effects operating in the two isomers, and a preferred conformation (causing magnetic non-equivalence of the t-Bu group) for the cis (t-Bu/H) isomer (76) has been postulated (see Chapter 3, Section (viii)(b)). The stereochemical arrangement of the aminopropene (86) was designated from thermodynamic considerations of the relative

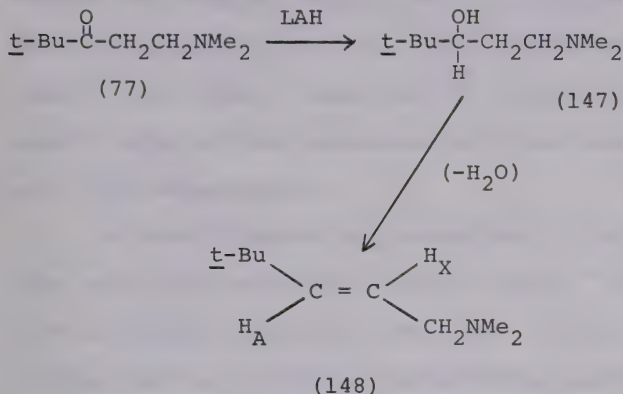
stabilities of this compound and its corresponding trans (t-Bu/H) isomer.

Initially, the benzyl compounds (76 and 79) were considered, and it was decided to use Tobey's (1969) direct substitution method; both of the aminobutene isomers are sterically crowded to a significant extent and indeed, the very existence of the conformation proposed for the cis compound (76) depends upon this assumption (see Chapter 3); thus, it was considered more advantageous to use the direct method where the appropriate σ values might compensate rather than propagate the σ 'constant' uncertainties (see earlier) produced by the steric clashing within these molecules.

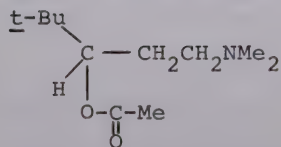
Before Tobey's method could be used, it was necessary to obtain shielding constants for the t-Bu group because no Z or σ values were available in the literature for this grouping. trans-1-t-Butyl-3-dimethylaminoprop-1-ene (148) was selected as a suitable compound with which to obtain the required cis or trans σ values for this group. A first order (AX) vinylic spectrum was anticipated for the propene (148), and knowing the quantitative shielding effects of the protonated dimethylamino function from the earlier work, it was hoped to evaluate meaningful cis and trans $\sigma_{\text{t-Bu}}$ values.

Synthesis of the required propene was intended by the reaction route given below and the initial reduction

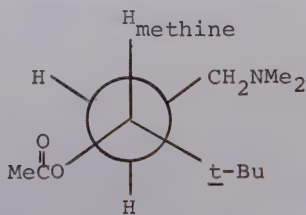
of the aminoketone (77) to the secondary alcohol (147)



proceeded smoothly and in good yield. Treatment of the latter with an acetic-hydrochloric acid mixture in an attempt to dehydrate the substrate to the propene (148) only resulted in the isolation of the acetate derivative (149). The PMR spectrum of the latter (see experimental) exhibited a doublet of doublets for its methine proton which indicated the existence of a preferred conformation as shown in the Newman diagram (149a).



(149)

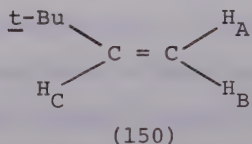


(149a)

This conformer allows dihedral angles of 60 and 180° between the coupled methine and C₂ methylene protons which according to Karplus' (1959; 1963) relationship (see p. 150) should result in the vicinal coupling constants being of the same order to those observed (3.5 and 9 Hz respectively).

A more vigorous acid-catalysed elimination reaction using 85% sulphuric acid at 100-110° led to oxidative decomposition of the precursor. Milder acid conditions for the attempted dehydration reaction were also tried (40% H₂SO₄) and although no pure products were isolated, there was no positive trace of the required propene (148) and it appeared that Wagner-Meerwein rearrangement of the t-Bu group had occurred (PMR evidence). Similar carbonium ion rearrangement products were isolated when elimination of the precursor alcohol was attempted using phosphorus pentachloride.

Hence, attention was turned to other possible t-Bu alkenes which might be used to obtain the relevant shielding constants for the t-Bu group. The commercially available 3,3-dimethylbut-1-ene (150) (Aldrich Chemicals)



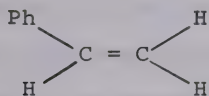
appeared to be a suitable standard compound as comparison of the vinylic shifts of this molecule with those of ethylene itself would allow calculation of the cis, trans, and gem σ_{t-Bu} parameters in an unhindered, freely rotating situation.

The vinylic region of the 60 MHz spectrum of the but-1-ene (150) in $CDCl_3$ was of the ABC type with 11 peaks being evident (see experimental). The corresponding 100 MHz spectrum (also in $CDCl_3$) produced a vinylic spectrum with a pseudo AMX appearance i.e. three quartets appeared in the low field area. The latter spectrum therefore appeared to be of the 'weakly coupled' ABC category (Mathieson 1967) in which the coupling constants between the protons were significantly smaller in magnitude than the chemical shift differences, although the appropriate ratios were still too small to create a true first-order spectrum. Nevertheless, the degree of mixing in such spectra is small and the combination lines become extremely weak compared to the fundamental absorptions and the A, B and C quartets can be readily recognised. In such cases, treatment of the spectrum as if it were first order leads to very reasonable approximations to the true chemical shifts and coupling constants values (Mathieson 1967). In 'strongly coupled' ABC systems (those in which J values between the protons are of the same order or exceeds the difference in their chemical shifts), first order treatment

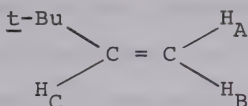
can be grossly misleading.

We decided to check this approach for a weakly coupled ABC system for which the real chemical shift values derived by a mathematical analysis were available. Comparison of values obtained by a simple first order treatment of the spectrum would be compared to the true resonance positions.

The published spectrum of styrene (102) (Bovey 1969), complete with calculated vinylic shifts, was very similar in overall appearance to 3,3-dimethylbut-1-ene (150) and a first order analysis gave chemical shifts for



(102)



(150)

the three vinylic protons which were within ± 5 Hz (at 60 MHz) of the true values. Suitably encouraged, we then applied a first order treatment to the vinylic quartets present in the 100 MHz spectrum of the but-1-ene (150). A line diagram of this region is shown in Figure 15.

The H_C proton was assigned to the low field quartet (consisting of lines 9, 10, 11 and 12) which was slanted towards the H_A and H_B signals. This quartet contained the two largest (trans and cis) of the three inter-vinylic coupling constants of the ABC system and the chemical shift of the H_C proton was obtained by assessing

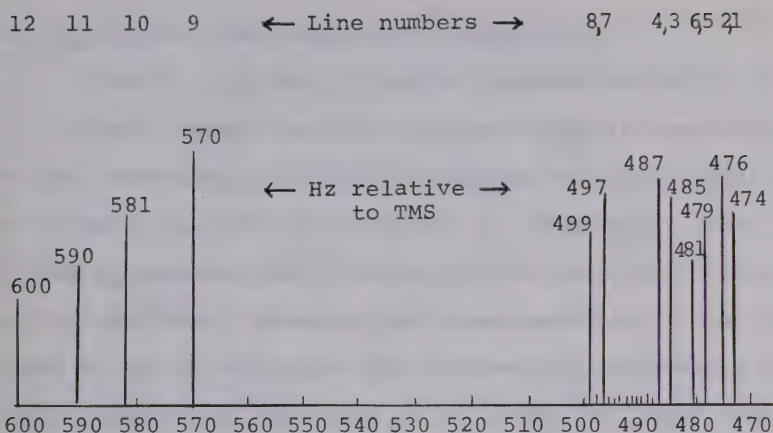
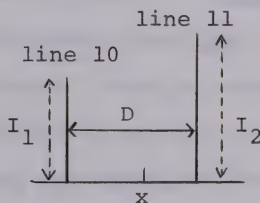


Figure 15. 100 MHz line diagram of the vinylic region of 3,3-dimethylbut-1-ene in CDCl_3 .

the centre of gravity (X) between the two innermost peaks (11 and 10); the relative intensities of the two lines (I_1 and I_2) separated by a distance D (see below) were



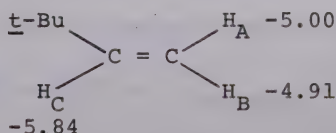
taken into account so that $X = \frac{I_2}{I_1} (D-X)$. This correction was applied to produce a more realistic chemical shift value from the first order analysis (Bigham 1970). Thus, $\nu_C = 584$ Hz at 100 MHz or -5.84 ppm.

An attempt to decouple the H_C protons from the H_A and H_B nuclei (to form an upper field AB quartet) failed due to the wide spread of the H_C signal. Hence, the H_A

and H_B quartets were separately considered.

The H_A (cis vinylic proton) quartet was split by the largest (trans) and the smallest (gem) in magnitude of the intervinylic coupling constants and thus consisted of lines 5, 6, 7 and 8 of Figure 15. This meant that the H_A and H_B quartets were overlapping in the vinylic region of the spectrum. However, the inter-relation of the four lines of the H_A multiplet was conclusively emphasised by the broadening of each peak ($J \sim 0.1$ Hz, as judged from 100 MHz sweep width expansion) by long-range (5-bond) coupling of the H_A proton to the t-Bu nuclei. Determination of the centre of gravity of the H_A quartet gave $\nu_A = 501.6$ Hz at 100 MHz or -5.00 ppm.

Finally, the H_B quartet (trans vinylic proton), which was split by the intermediate (cis) and smallest (gem) of the three intervinylic coupling constants, was assessed to have $\nu_B = 491.2$ Hz at 100 MHz or -4.91 ppm. Subtraction of the -5.32 ppm value for ethylene from the approximate H_A , H_B and H_C vinylic shifts of 3,3-dimethylbut-1-ene (147) gave:

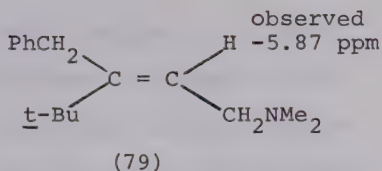
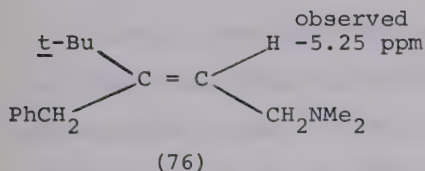


$$\sigma_{\text{cis t-Bu}} = -5.00 - (-5.32) = \underline{+0.32}$$

$$\sigma_{\text{trans t-Bu}} = -4.91 - (-5.32) = \underline{+0.41}$$

$$\sigma_{\text{gem t-Bu}} = -5.84 - (-5.32) = \underline{-0.52}$$

Thus, the predicted vinylic shift values for the cis and trans (t-Bu/H) but-2-enes (76) and (79) could now be evaluated.



Considering the cis isomer (76), from Tobey's equation:

$$\begin{aligned}
 \delta_{\text{C}=\text{C}-\text{H}} (76) &= -5.27 + \sigma_{\text{cis } \text{t-Bu}} + \sigma_{\text{trans } \text{PhCH}_2} \\
 &\quad + \sigma_{\text{gem } \text{CH}_2^+\text{NMe}_2} \\
 (\sigma_{\text{trans } \text{PhCH}_2} &= +0.17, \text{ see p. 173}) \\
 (\sigma_{\text{gem } \text{CH}_2^+\text{NMe}_2} &= -0.83, \text{ see p. 175})
 \end{aligned}$$

Substituting,

$$\begin{aligned}
 \therefore \delta_{\text{C}=\text{C}-\text{H}} (76) &= -5.27 + (+0.32) + (+0.17) + (-0.83) \\
 &= \underline{-5.61} \text{ (observed } -5.25)
 \end{aligned}$$

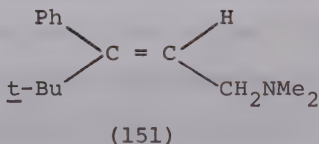
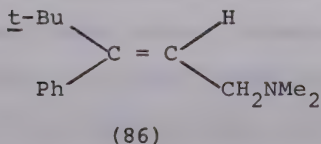
Similarly, for the trans isomer (79):

$$\begin{aligned}
 \delta_{\text{C}=\text{C}-\text{H}} (79) &= -5.27 + \sigma_{\text{cis } \text{PhCH}_2} + \sigma_{\text{trans } \text{t-Bu}} + \sigma_{\text{gem } \text{CH}_2^+\text{NMe}_2} \\
 (\sigma_{\text{cis } \text{PhCH}_2} &= +0.15, \text{ see p. 173})
 \end{aligned}$$

$$\begin{aligned}\delta_{\text{C}=\text{H}} (79) &= -5.27 + (+0.15) + (+0.41) + (-0.83) \\ &= \underline{-5.54} \text{ (observed } -5.87)\end{aligned}$$

Hence, both predicted vinylic shifts (-5.61 and -5.54 ppm) were considerably different to either of the two observed values (-5.25 or -5.87 ppm) and no definite conclusions as to the configurations of the isomers could be made. It appears that the steric and electronic interactions between the t-Bu group and two other substituents in trisubstituted vinylic molecules are too complex and diverse for such a simplified approach. In addition, the close similarity (+0.32 and +0.41) of the cis and trans $\sigma_{\text{t-Bu}}$ values, which are within the ± 0.10 ppm uncertainty of the method (Tobey 1969), also contributes to the ineffectiveness of the additivity principle to differentiate between isomers such as compounds (76) and (79).

Nevertheless, the predicted resonance positions of the vinylic protons of the aminopropene (86) and its trans (t-Bu/H) isomer (151) were still calculated (the cis (t-Bu/H) configuration of (86) had been assigned after



consideration of the likely relative stabilities of the two isomers) (see p. 95):

$$\text{Thus, } \delta_{\text{C}=\text{C}-\text{H}} (86) = -5.27 + \sigma_{\text{cis } \underline{\text{t}}\text{-Bu}} + \sigma_{\text{trans Ph perturbed}} \\ + \sigma_{\text{gem CH}_2\text{NMe}_2^+}$$

$$(\sigma_{\text{trans Ph perturbed}} = +0.01, \text{ see p. 179})$$

Substituting,

$$\therefore \delta_{\text{C}=\text{C}-\text{H}} (86) = -5.27 + (+0.32) + (+0.01) + (-0.83) \\ = \underline{-5.77}$$

Similarly,

$$\delta_{\text{C}=\text{C}-\text{H}} (151) = -5.27 + \sigma_{\text{cis Ph}} + \sigma_{\text{trans } \underline{\text{t}}\text{-Bu}} + \sigma_{\text{gem CH}_2\text{NMe}_2^+}$$

$$(\sigma_{\text{cis Ph}} = -0.39, \text{ Tobey 1969})$$

Substituting,

$$\therefore \delta_{\text{C}=\text{C}-\text{H}} (151) = -5.27 + (-0.39) + (+0.41) + (-0.83) \\ = \underline{-6.08}$$

Hence, the observed vinylic shift (-5.94 ppm) of the aminopropene which had been isolated in our studies was almost midway between the two predicted values (-5.77 and -6.08 ppm). Furthermore, the ± 0.10 ppm uncertainty of the method (Tobey 1969) made both of the calculated figures correlatable with the observed value so that once again a firm configurational designation to a $\underline{\text{t}}\text{-Bu}$ substituted aminoalkene could not be made using Tobey's method.

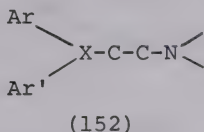
The overall molecular interactions in such structures appear to drastically disturb the simple additivity principle of the various shielding effects of the substituents. Finally, it should be noted that it is doubtful whether the 'single model compound' approach would be any more fruitful; 'conversion' of a disubstituted olefinic model (containing a t-Bu group) to the required trisubstituted compound would again take no account of the complex steric interactions of the 'introduced' group with the other substituents.

CHAPTER 6

A GENERAL THEORY FOR THE POSSIBLE STRUCTURAL AND CONFORMATIONAL REQUIREMENTS OF HISTAMINE ANTAGONISTS

A GENERAL THEORY FOR THE POSSIBLE STRUCTURAL AND CONFORMATIONAL REQUIREMENTS OF HISTAMINE ANTAGONISTS

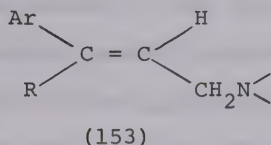
The majority of compounds which effectively antagonise histamine at low dose levels may be described by the general formula (152) where Ar is aryl (including



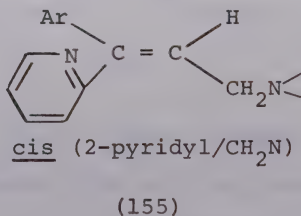
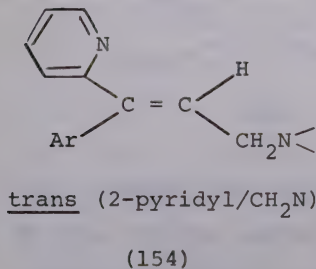
heteroaryl), Ar' is aryl or arylmethyl, and X is nitrogen, C-oxygen or saturated carbon; X-C in (152) may be replaced by a carbon-carbon double bond and the terminal nitrogen atom is part of a tertiary acyclic or alicyclic basic group (Barlow 1964; Burger 1963; Grisvold and Wilson 1962). If it is assumed that the aryl function(s) and the basic group are the essential pharmacodynamic moieties of these molecules, it is probable that their relative dispositions at the histamine receptor are similar in all active compounds if these antagonists have related modes of action.

A clue to the optimal arrangement may be gained by examination of the stereochemistry of antihistamines in which the key groups are attached to a carbon-carbon double bond. In these alkenes, the relative dispositions of molecular components are greatly restricted in comparison with

derivatives based on the general formula (152) itself. The two known groups of alkene compounds with antihistaminic properties, namely 4-aminobutenes and 3-aminopropenes have been studied and discussed in Chapters 3 and 4, respectively, of this thesis. The most potent isomers of both groups possess the common structure (153) rigidly orientated in

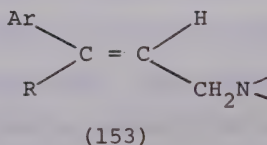
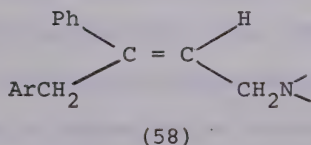


the same manner and it is proposed, in view of the high potency of these compounds and the activity fall which follows a configurational change, that this unit is an optimal conformation for activity in antihistaminic agents. It should be noted that in the 3-aminopropene isomers (see Chapter 4, section (i)) the arrangement (153) can exist in both the cis and trans compounds (154 and 155) (since Ar = 2-pyridyl as well in structure 153). Adamson and his group (1951)



claimed that high and specific antihistaminic activity is shown only by the trans (2-pyridyl/CH₂N) isomers but pharmacological data on our own examples of this series was not wholly in support (see p. 128). Hence there is some doubt as to the specificity in regard to the nature of the aryl group cis to the vinylic hydrogen in 3-amino-propene isomers. An answer to the latter problem is not crucial to the following general arguments as the stereochemical features of both the cis and trans aminopropene isomer types will be very similar (owing to the close steric characteristics of the aryl and 2-pyridyl rings).

The overall shape of the more potent aminoalkene antihistaminics will now be considered in terms of probable conformations. In the 4-aminobutene series the cis (H/Ph) aminobut-2-enes (58) have been shown to possess steric features which are optimal for activity (see Chapter 3). Thus R = CH₂Ar and Ar = Ph in the common structural (153)



unit proposed for high potency. Within these isomers, the Ph ring and the carbon-carbon double bond are approximately coplanar (physical evidence see p. 37); in addition, to minimize non-bonded interactions, the plane of the second

aryl group (Ar) attached to methylene must lie at about 70° to the $\text{Ph}-(\text{C}=\text{C})$ plane (as indicated from examination of Catalin and Framework Molecular models). Thus the net shape of the cis (H/Ph) aminobut-2-ene molecule in its preferred conformation, is shown diagrammatically in Figure 16.

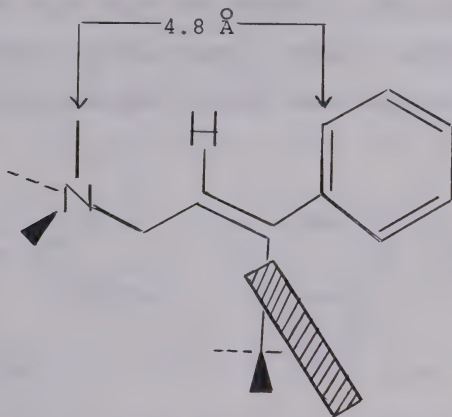
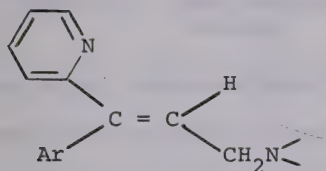


Figure 16. The preferred conformation of cis (H/Ph) aminobut-2-ene isomers.

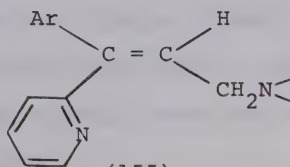
The planes of the two aromatic rings are thus nearly at right angles while the components of the $\text{ArC}=\text{CHCH}_2\text{N}$ unit lie close to a mean molecular plane. The distance between nitrogen and an ortho aromatic carbon atom shown in Figure 16 relates to the work of Kier (1968) on histamine and Triprolidine (14), discussed later. In trans (H/Ph) analogues of (58), of much lower antihistaminic potencies (see Chapter 3), the Ph and carbon-carbon double bond planes greatly diverge; conformers are probable in

which the benzyl aromatic ring lies in a similar plane to the $C=CHCH_2N$ feature but the comparable N-Ortho aromatic carbon distance is at least $1 \overset{O}{\text{\AA}}$ unit greater than that of the cis isomer.

In isomeric 3-aminopropenes (154 and 155) of the Triprolidine type only one aromatic ring may be coplanar with the alkenic double bond. Models indicate that aryl cis to vinylic hydrogen within each structure is more



(154)



(155)

probable as the coplanar group and this has been confirmed by physical methods (UV data, Adamson et al. 1957; also PMR data see p. 122). The preferred conformation of this class shown in Figure 17 (see also Barlow 1964) is thus very similar to that of the 4-aminobut-2-enes (see Figure 16) the only difference being the absence of an aryl methylene feature in the former.

Formally less rigid antihistaminic drugs will now be examined to establish whether or not they are likely to adopt conformations in which their aryl and CH_2N features are disposed in a similar fashion to the aminoalkene

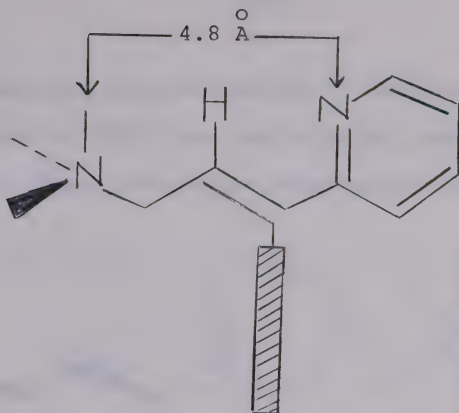
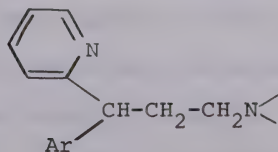


Figure 17. The preferred conformation of 3-aminopropene isomers.

preferred conformations depicted in Figures 16 and 17 (Hite and Shafi'ee, 1967, have pointed out that there is no evidence that conformationally mobile antihistamines are bound in their most stable conformations).

1. Pheniramines

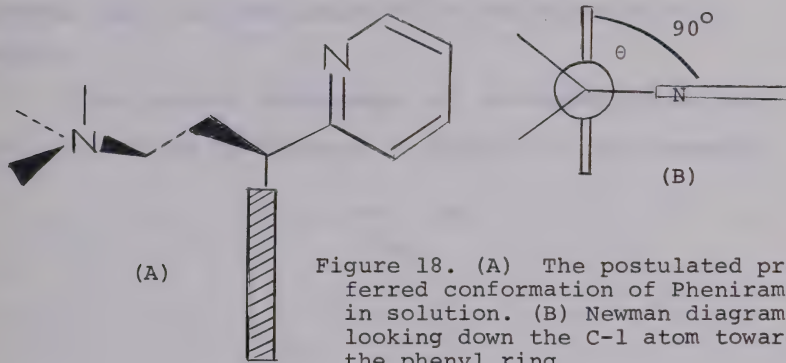
These compounds have the general formula (156) and may be regarded as hydrocarbon analogues of the 3-amino-propenes (154 and 155). In these models, 2-pyridyl is made



(156)

the aryl group most nearly planar with the alkylamine chain (by analogy with Triprolidine (14) whose 2-pyridyl and tertiary amino group are in the same molecular plane). The

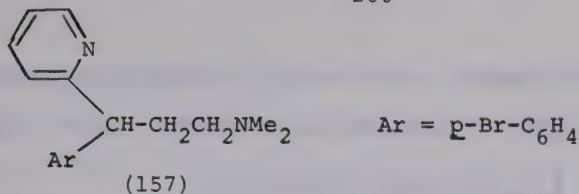
three-dimensional representation of this conformation is shown in Figure 18(A), and the dihedral angle* θ between the aromatic rings is not far removed from 90° , as shown



by Figure 18(B). A model in which the near planar $\text{ArCH}(\text{CH}_2)_2\text{N}^<$ unit is maintained may also be made when the inter-aryl dihedral angle is greater than 90° ("butterfly" arrangement of Ph_2CH) but non-bonded interactions are judged to be greater in this conformation.

Dr. M. James and Mr. G. Williams of the Department of Biochemistry, University of Alberta, have carried out an X-ray crystallographic study of Brompheniramine (157) and have kindly informed us of some of their preliminary results. The dihedral angle between the planes of the aromatic rings was found to be $103^\circ 7'$, a value somewhat

* Defined as the angle between planes containing a) C-1 and C-2 of one aryl group and b) C-1 and C-2 of the other aryl group, with the quaternary carbon atom common to both.



greater than the postulated 90° of the molecule as a solute.

The spatial arrangement of Brompheniramine in the solid state is depicted in Figure 19; both aromatic

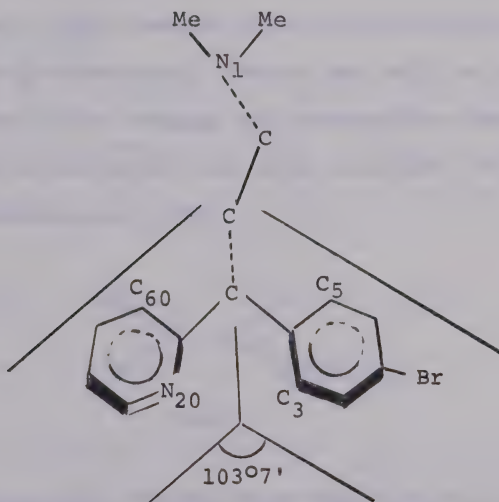


Figure 19. Ring orientations of Brompheniramine (157) maleate in the crystalline state.

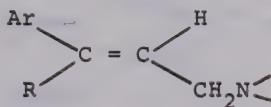
functions appear capable of acting within a near planar Ar/NMe_2 unit in much the same way to the aromatic groups contained in the preferred conformers of the aminoalkenes shown in Figures 16 and 17.

However, the calculated interatomic distances between the ortho ring atoms (C_3 , C_5 , C_{60} or N_{20}) and the

acyclic nitrogen (N_1) (see below) suggest that the side-chain is not symmetrically disposed between the rings

<u>Interatomic distances in $\overset{\circ}{\text{\AA}}$</u>	
N_1-C_5	4.98
N_1-C_3	5.40
N_1-C_{60}	5.24
N_1-N_{20}	6.145

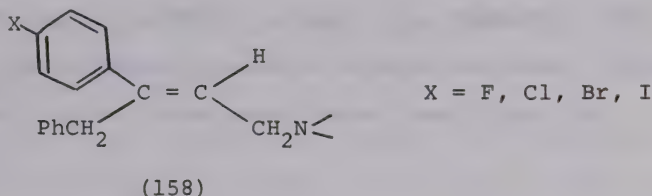
and that it has a bias towards the non-heterocyclic function. Thus the p-bromophenyl moiety may well be the aromatic feature which occupies and antagonises the receptor area which is filled by the aryl ring (Ar) of the active aminoalkenic structures (153).



(153)

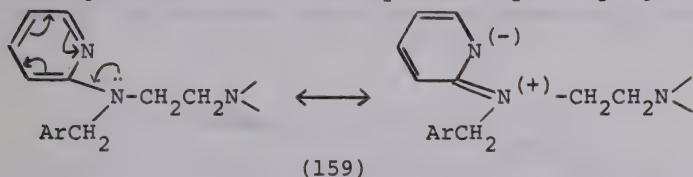
This conclusion follows from the fact that of the four ortho atom (C or N) to N_1 distances of Brompheniramine (see Figure 19), the one closest to the N_1 to N distance of Triprolidine ($4.8 \overset{\circ}{\text{\AA}}$) is the N_1-C_5 value ($4.98 \overset{\circ}{\text{\AA}}$), the N_1-N_{20} and N_1-C_{60} separation being much greater. The possible significance of these interatomic distances in regard to antihistaminic properties, as proposed by Kier (1968), is discussed at the end of this Chapter.

Such observations suggest that it would be of great interest to prepare a series of *p*-halogenophenyl cis (H/Ar) but-2-enes (158) and to assess their antihistaminic activities.



2. Ethylene Diamines

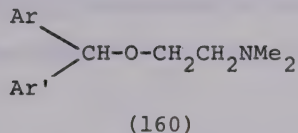
These compounds depicted in the general formula (159) (2-pyridyl being replaced by phenyl in some derivatives e.g. Antergan (24)), have an aryl and arylmethyl group linked



to one of the diamine nitrogen atoms; restricted rotation about the N-aryl bond is probable as a result of resonance interactions as shown. Once again it is possible to construct a molecular model of (159) which is markedly similar to the 4-aminobut-2-ene conformation (see Figure 16) except that the $\text{CH}_2-\text{N}^{\dagger}=\text{C}$ (planar nitrogen) unit replaces the carbon-carbon double bond of the latter. The planar nitrogen form is probable on the grounds of minimum steric interactions and also maximum operation of N-Ar resonance effects.

3. Diphenylhydramines

The variant of the general structure (160) in which X is C-oxygen and the terminal carbon atom is attached to two aromatic groups (e.g. Benadryl (160); $\text{Ar}=\text{Ar}'=\text{Ph}$) similarly yields a strain-free model (Figure 20), akin to the 4-aminobut-2-ene (see Figure 16), in



which the ether oxygen bonds lie close to the plane of one of the aromatic rings with an inter-aryl dihedral

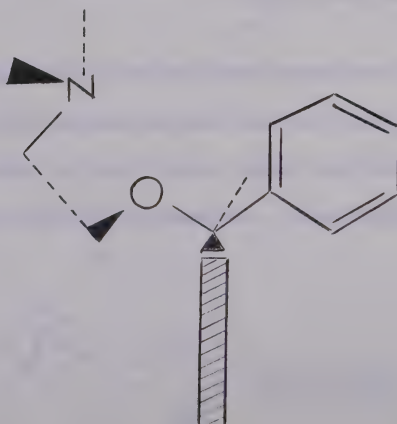
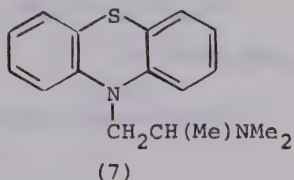


Figure 20. Strain-free conformational model of Benadryl comparable to the preferred conformation of cis (H/Ph) aminobut-2-ene antihistamines.

angle near 90° . Harms and coworkers (1966) have proposed an 'active' diphenylhydramine conformation similar to Figure 20 and cited IR and UV spectroscopic evidence for the coplanarity of oxygen and the *p*-tolyl substituent in 4-methyldiphenylhydramine (160; Ar=Ph, Ar'=p-Me-C₆H₄).

4. Cyclic Derivatives

These are formed when the two aryl substituents of (152) are fused at *o*-positions to sulphur or carbon atoms. In phenothiazine derivatives (e.g. Promethazine 7) a model



may be constructed in which the β -aminoethyl side chain attached to ring nitrogen and one of the aromatic rings lie more or less in one plane with the second aromatic ring removed from this dimension (see Figure 21).

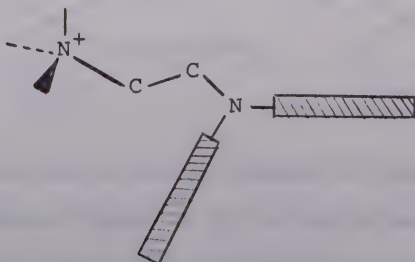
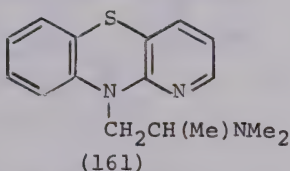


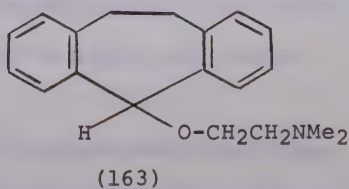
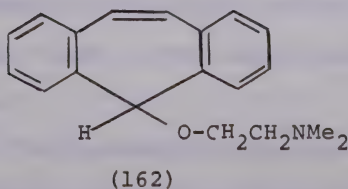
Figure 21. Strain-free butterfly conformation of Phenothiazines.

However, the dihedral angle between the planes of the aromatic rings is significantly greater (ca. 120°) than the close to 90° angle in the 4-aminobut-2-ene (Figure 16), as a result of the rings being constrained to a "butterfly" conformation by their linkages to the heterocyclic atoms (the alternative "butterfly" conformation is unlikely on account of steric interactions between the N-side chain and adjacent aromatic hydrogen atoms). Similar



considerations of molecular shape apply to Isothipendyl (161).

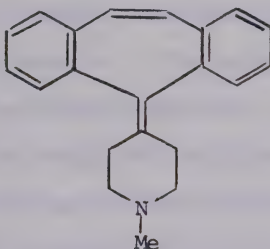
In the fused ring derivatives (162 and 163) the angle between the aromatic planes is less than that in the



phenothiazines and molecular models of these compounds closely resemble Figure 20 in having a near planar $>\text{NCH}_2\text{CH}_2\text{OCH-Ph}$ unit with the second ring approximately

at right angles to this feature (Harms et al. 1966). These derivatives can be regarded as analogues of Benadryl (160; Ar=Ar'=Ph) and both are significantly more active than the parent compound in which the two rings are unconstrained.

The recently introduced antihistamine, Cyproheptadine (57) also has a shape similar to (162) and



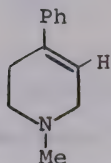
(57)

(163), except that the planes of the aminoalkyl residue and one aromatic ring do not coincide so closely since they are held apart by the double bond linkage within the system.

The preceding account has demonstrated that many antihistamine drugs in clinical use may adopt conformations similar to those of the model aminoalkene antihistaminics without serious non-bonded interactions being generated. If the overall molecular arrangements of these compounds typified in Figures 16 and 17 be accepted as specially

conductive to the blockade of histamine receptors, it appears most reasonable to postulate that the near-planar aminoalkyl-aryl section of the antagonist molecule occupies the histamine receptor itself, since this unit has a similar shape to and dimensions of the histamine molecule (see below). It is assumed that histamine sites occupied by protonated amino and the imidazole ring of the agonist probably interact with the protonated side chain nitrogen and the planar aryl group respectively of the antagonist. The second aromatic feature of the molecule (antiplanar with the rest of the molecule) is assumed to occupy an additional receptor area which is not implicated in the uptake of histamine itself (the concept of antagonists utilising more receptor sites than the molecules which they antagonise has been discussed by Ariëns and Simonis 1964). Speculations along these lines have previously been made by Harms and coworkers (1966) in respect of 4-methyldiphenylhydramines.

The importance of having two aromatic groups present in an antihistaminic compound is emphasized by the negligible activity (only 7% inhibition of histamine-induced contractions of isolated guinea-pig ileum after 6 min. at 0.10 $\mu\text{g/ml}$ solution concentration) of the tetrahydropyridine (164), which contains the near planar $\text{ArC}=\text{CHCH}_2\text{N} <$ unit



(164)

of the potent aminoalkenes, while results upon the t-Bu derivatives (see p. 110) underline the importance of the planar feature itself. In the latter derivatives, all of low potency (see Table XVIII), coplanarity of the aromatic and double bond planes is seriously disturbed by the bulky t-Bu substituent.

Kier (1968) has proposed favoured trans and gauche NH_3^+/Ar conformations for histamine (1) (see next Chapter) based on molecular orbital calculations and has suggested that the similar N to N interatomic distances of the trans conformer (4.55 \AA) (see Figure 22) and Triprolidine (4.8 \AA) may be of significance in explaining the latter compound's

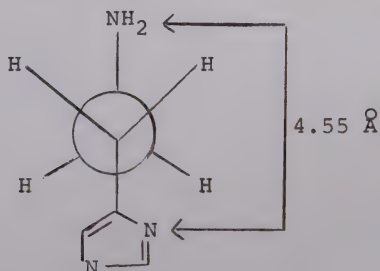


Figure 22. Newman diagram of the trans conformer of histamine looking down the aminoethyl sidechain of the molecule.

antagonist properties. It is of interest that the 4.8 Å distances between the side-chain nitrogen atom and an aromatic ortho atom (N or C) comprising the near planar feature of the conformations proposed for the cis (H/Ph) aminobut-2-enes and Triprolidine type aminopropenes (see Figure 16 and 17 respectively) are all close to the histamine N to N distance (4.55 Å) specified above. This observation shows how the shape and dimensions of the histamine molecule may be reproduced in antihistaminic agents. Finally, it should be noted that many antihistamines are active at about one hundredth the concentration of histamine required to induce contraction of the guinea-pig ileum (Barlow 1964). This observation provides some evidence that the additional aromatic features of various potent antihistaminics significantly improves their binding and 'fit' at the H₁ receptor compared to histamine itself.

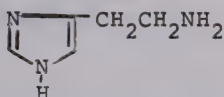
CHAPTER 7

CONFORMATIONAL STUDIES OF HISTAMINE AND VARIOUS ANALOGUES
AND ATTEMPTS TO INTRODUCE THE IMIDAZOLE NUCLEUS INTO AN
ANTI-HISTAMINIC STRUCTURE

CONFORMATIONAL STUDIES OF HISTAMINE AND VARIOUS ANALOGUES
AND ATTEMPTS TO INTRODUCE THE IMIDAZOLE NUCLEUS INTO AN
ANTIHISTAMINIC STRUCTURE

(i) PMR Conformational Studies of Histamine and Various
Analogues Substituted in the Terminal N Atom or the
Ethyl Sidechain

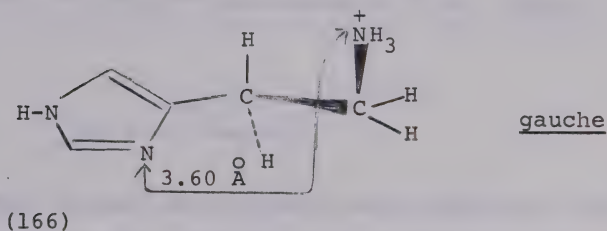
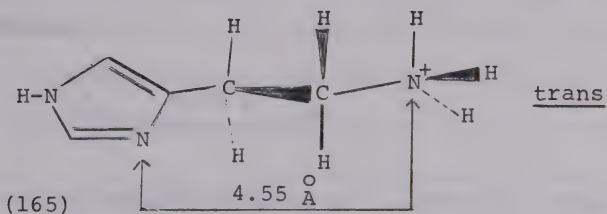
Our interest in the conformational preferences of histamine (1) was initiated by the theoretical work of Kier reported during 1968; this author had carried out



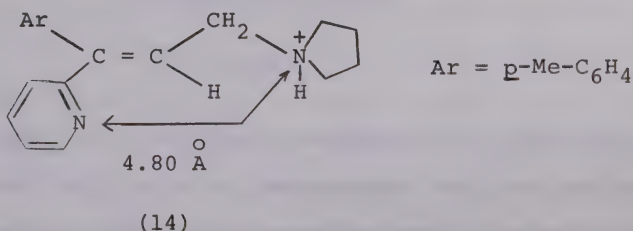
(1)

extended Hückel molecular orbital calculations on the histamine molecule and had revealed (on the basis of calculated minimum energies) that two conformations of nearly equal preference were apparent. These were the trans (or anti) (165) and gauche (166) rotamers depicted below. Kier postulated that the dual in vivo agonist action of histamine (guinea-pig ileum contractory effect or gastric secretory stimulation) was due to each preferred conformation interacting specifically at one of the two receptor types (H_1 or H_2) known for histamine.

He differentiated which of the two histamine conformations was associated with the H_1 receptor by comparing

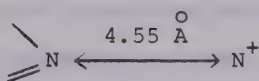


certain molecular features of the potent antihistaminic Triprolidine (14) with the trans rotamer of histamine (165). Triprolidine, in common with other antihistamines,

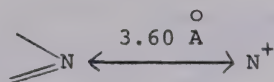


is considered to antagonise only those effects of histamine mediated via the H₁ receptor (Ash and Schild 1966); as the internitrogen distance of Triprolidine in its preferred conformation is 4.80 Å (compared to the calculated internitrogen distance of 4.55 Å for histamine in its trans

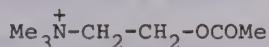
conformation) Kier concluded that the H_1 receptor is complementary to the N-N relationship obtaining in the trans conformer:



In addition, he predicted that the H_2 receptor should be complementary to the N-N relationship of the gauche conformer:



A year earlier Martin-Smith and coworkers (1967) reviewed evidence for proposals that the dual action of acetylcholine (167) may be attributed to the specific action of two distinct conformers acting on either the

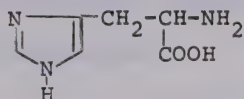


(167)

'muscarinic' or 'nicotinic' receptors; in this case Kier (1967) was again able to demonstrate that two preferred conformers of close total energies could theoretically exist. Culvenor and Ham (1966), however, showed by a PMR approach that the gauche form of acetylcholine predominated in aqueous solution and later Canepa et al. (1966) proved by an X-ray analysis that this

conformation was preferred in the solid state.

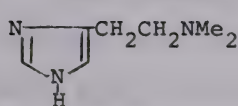
In the case of histamine, X-ray studies (Palenik and Veidis 1969; Palenik et al. 1969) have revealed that histamine (as the acid phosphate monohydrate) existed solely in the trans conformation (165) in the solid state; this contrasted to the cis conformation of the amino-acid, histidine (168), in the same phase. Accordingly, these authors speculated that the same conformational differences



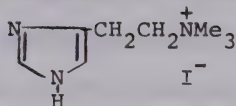
(168)

between the two compounds might also exist in solution.

We decided to investigate the conformational preferences of histamine as a solute under close to physiological conditions and to compare results with Kier's theoretical conclusions. PMR spectroscopy appeared to be the obvious technique with which to pursue this study following Culvenor and Hams' (1966) successful application of the method to acetylcholine. It was also intended to prepare and conformationally analyse 4(5) (dimethylaminoethyl)imidazole (169), the quaternary methiodide (170) of the latter, and α -methylhistamine (171). The dimethylamino derivative and its methiodide have distinctly diverse



(169)



(170)



(171)

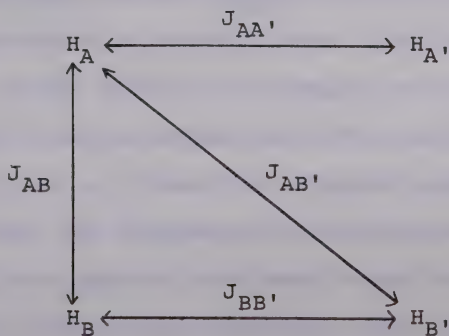
agonist properties (see later) which were thought possibly to be correlatable with the different conformational equilibria of each of the two compounds. Furthermore, α -methylhistamine is known to be a weak agonist (see later) and it was therefore of additional interest to examine this compound using the PMR method.

(a) PMR Examination of Histamine in Aqueous Solution

Histamine (1) may be regarded as a 1,2-disubstituted ethane (with unlike substituents) which at room temperature will exist as a mixture of rapidly rotating and interconverting conformational isomers. Unless the rotation about the carbon-carbon single bond is restricted by some form of molecular interaction the observed coupling constants will be representative of the weighted mean of the couplings of the distinct isomers. This is the result of the exceedingly small (ca. 5 k cal/mole) energy required to rotate substituents about a saturated bond; even at low temperatures the signals from the individual isomers cannot be 'frozen out' in derivatives of this type (Thomas 1968).

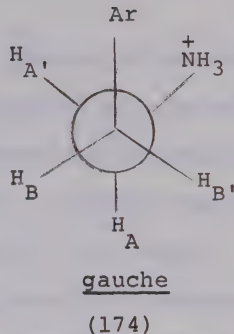
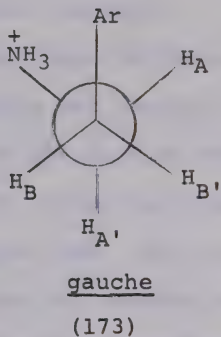
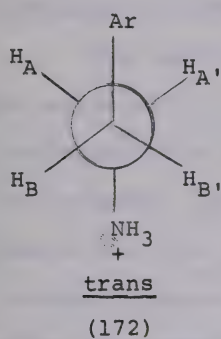
The bimethylene fragment of histamine comprises a 4-proton spin system described by the AA'BB' notation (Emsley et al. 1965; Bovey 1969) and within this portion of the molecule the individual nuclei of the AA' and BB' pairs are equivalent in the chemical shift sense and come to resonance at identical field positions. However, in the AA' pair, A and A' show finite geminal coupling and are unequally coupled to B (and B'). Thus the four nuclei forming the AA' and BB' pairs are magnetically non-equivalent. [N.B. The A_2B_2 notation is only used when both A nuclei are equally coupled to each B nucleus i.e. $J_{AB} = J_{AB'}$, and few molecules satisfy the latter criterion (Emsley et al. 1965)].

Thus, four coupling constants ($J_{AA'}$, J_{AB} , $J_{AB'}$, and $J_{BB'}$.) are involved in the 4-proton bimethylene spin system of histamine:



$J_{A'B} = J_{AB'}$
 $J_{A'B'} = J_{AB}$
 because of symmetry

J_{AB} and $J_{AB'}$ are the time-averaged coupling constants made up of contributions from the three staggered rotamers shown below.



(Ar = 4(5)-imidazolyl)

When there is no preference between the trans (172) and two equivalent gauche (173/174) forms, $J_{AB} = J_{AB'}$, because both of these average coupling constants will be made up of one trans and two gauche J contributions. If there is a predominance of one conformer then, obviously, $J_{AB} \neq J_{AB'}$.

AA'BB' spectra are complex and cannot be analysed by first order treatment and often contain a number of ambiguities, not least the frequent appearance of fewer lines than the theoretically anticipated number of 24; the latter such spectra have been termed as 'deceptively simple' (Abraham and Bernstein 1961; Jackman and Sternhell 1969) owing to their resemblance to first order spectra.

Moreover, AA'BB' systems form centrosymmetric* line patterns arising from the A and B group protons of the molecule so that only one half of the spectrum need be considered for spectral analysis.

The detailed analysis of these systems is outside the scope of this thesis but the D₂O spectra of histamine dihydrochloride at 100 MHz that we observed will presently be discussed. We were indeed fortunate to obtain the collaboration of Dr. Norman Ham (C.S.I.R.O., Division of Chemical Physics, Victoria, Australia) who had previously solved the acetylcholine conformational problem of PMR spectroscopy in association with Dr. Culvenor (1966).

Dr. Ham took N and L values (see below) from appropriate line separations according to Garbisch (1968) and by use of Bothner-By's LAOCOON computer program (1964) was able to carry out calculations using various chemical shifts and coupling constants to afford numerous theoretical PMR spectra of acetylcholine. This indirect 'iterative' approach was continued and values refined until a 'fit' of the calculated and observed spectra was obtained. By this means the precise L and N spectral parameters (see next page) were determined which led to

* the A and B portions themselves are not symmetrical as in AA'XX' spectra.

$$K = J_{AA'} + J_{BB'}$$

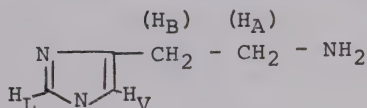
$$L = J_{AB} - J_{AB'}$$

$$M = J_{AA'} - J_{BB'}$$

$$N = J_{AB} + J_{AB'}$$

the finding of the gauche conformer predominating in solution.

In the case of histamine the actual spectrum of the dihydrochloride obtained at 100 MHz in D₂O solution is shown in Figure 23 and will now be discussed.



The undecoupled but expanded bimethylene region of the spectrum (determined at pH 7) is shown and the lack of symmetry about the mid-point of the line pattern is due to additional coupling by the higher field H_B nuclei with the vicinal (H_V) proton of the imidazole ring (see above). The chemical shifts (from external TMS) of the H_L and H_V protons were 884.6 and 775.3 Hz respectively and the cross ring coupling between the two nuclei was +1.2 Hz. In addition, the benzylic coupling between H_V and the H_B sidechain protons was -0.8 Hz. Dr. Ham was able to triple irradiate the histamine sample so that H_V (and H_L) were effectively decoupled from the H_B protons and the resulting

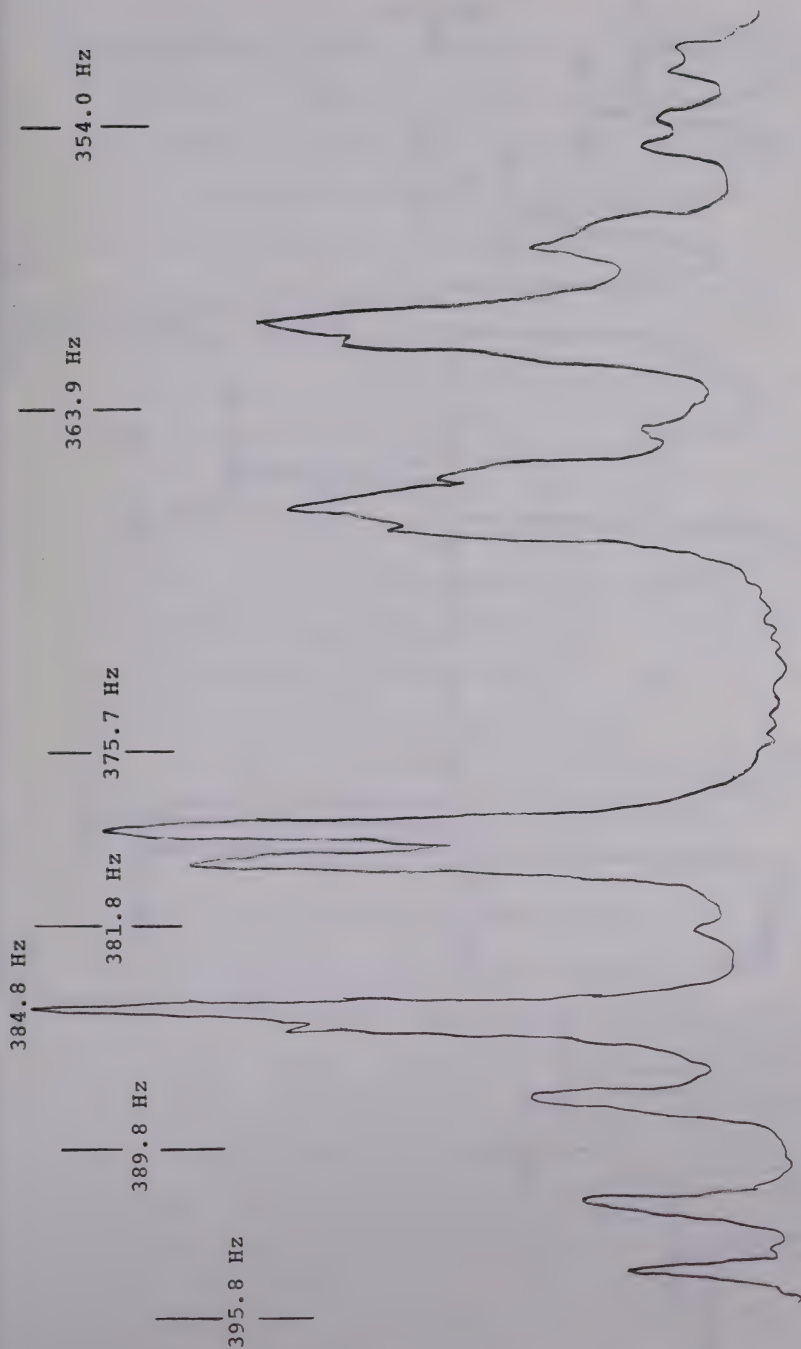


Figure 23. 100 MHz bimethylene region (100 Hz sweep width) of histamine dihydrochloride in D_2O adjusted to pH 7. External TMS was used as the reference.

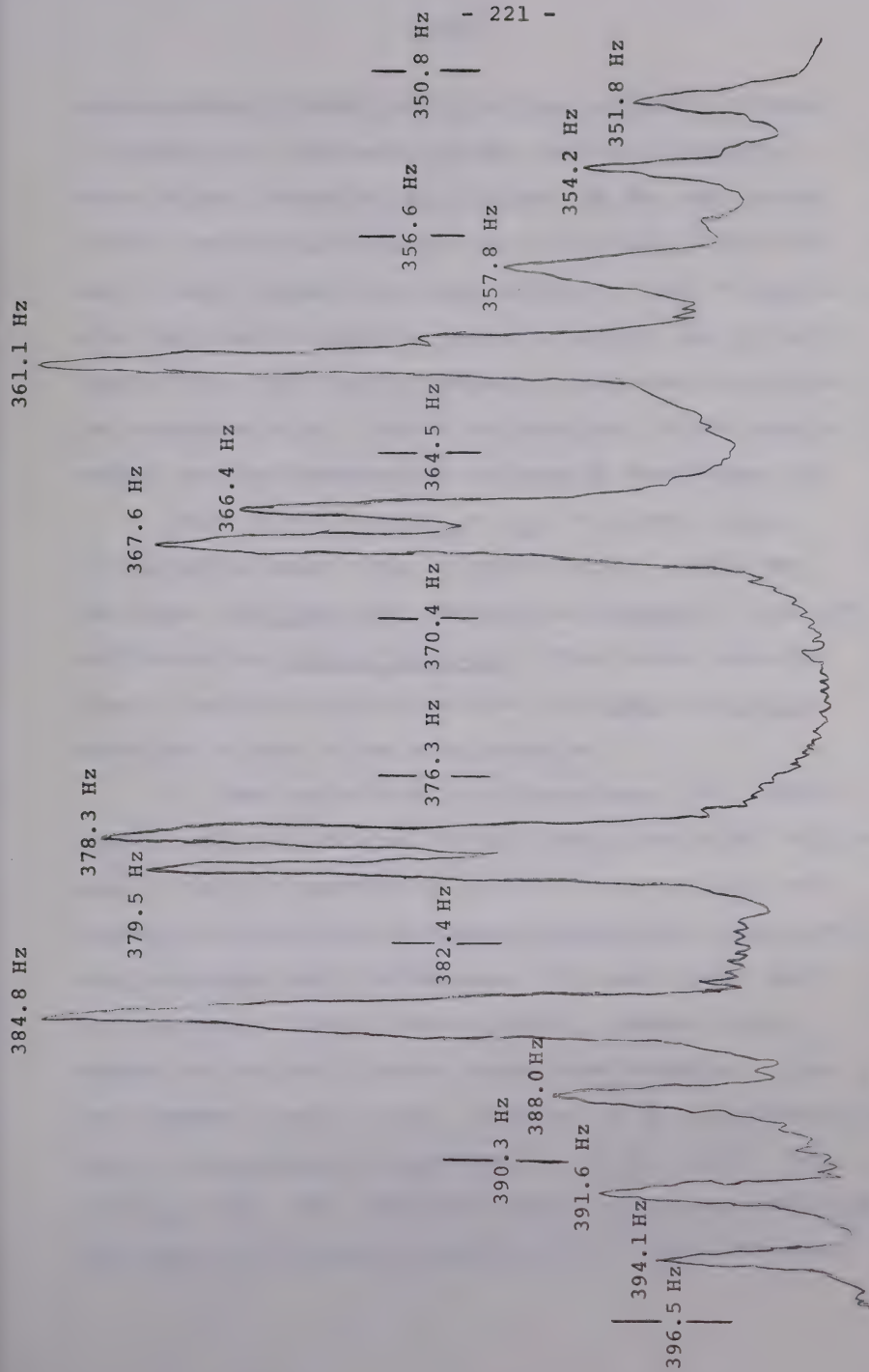


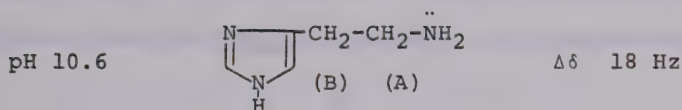
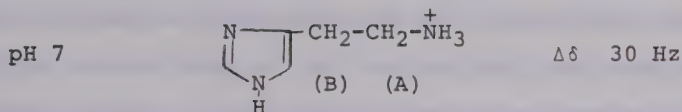
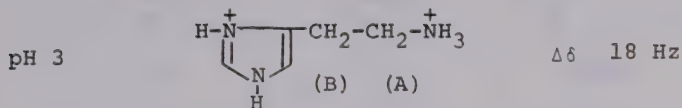
Figure 24. 100 MHz bimethylene region (100 Hz sweep width) of histamine in D₂O at pH 7 after triple irradiation (H_L, H_V decoupled). External TMS was used as the reference.

centrosymmetric bimethylene spectrum (at pH 7) is shown in Figure 24. This spectrum was used for a series of computerised iterative calculations (in the same manner as for acetylcholine) which gave the precise N (14.4 Hz) and L (zero) parameters; these values of L and N together with the observed benzylic coupling between the H_B and H_V protons were then used to compute a theoretical spectrum for histamine at pH 7 which was identical to the experimental spectrum recorded at the same pH (see Figure 23).

Thus, $L = 0$, i.e. $J_{AB} - J_{AB'} = 0$ (see p. 219), for histamine under close to physiological conditions, and hence the trans (172) and the two gauche (173 and 174) conformers are equally populated. This result supports Kier's theoretical postulate that the trans and gauche forms are of very close total energies.

Dr. Ham was also able to demonstrate that 100 MHz spectral changes occurred in the bimethylene AA'BB' multiplet of the D_2O spectrum as the pH of the solution was varied by the addition of sodium deuteroxide. The approximate methylene shift differences ($\Delta\delta$) (see below) were accountable in terms of the H_A and H_B chemical shift changes as various N centre ionisations occurred. Thus, the increased $\Delta\delta$ value at pH 7 compared to pH 3 is probably due to the progressive deprotonation of the planar ring nitrogen atom. This sequence causes a decreased deshielding influence on the higher field H_B protons which therefore

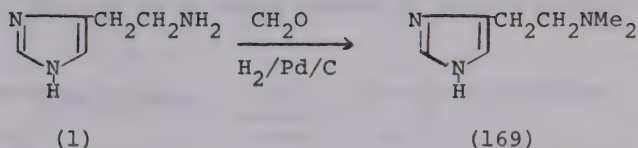
undergo upfield shifts to increase $\Delta\delta$. At pH 10.6,



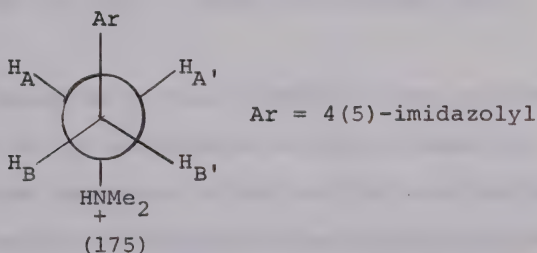
neither of the two amino nitrogen centres is protonated so that the H_A protons can also shift upfield which reduces $\Delta\delta$ back to a value of about 18 Hz.

(b) Preparation and PMR Examination of 4(5) (Dimethylaminoethyl)imidazole (169)

A search of the literature revealed that 4(5) (dimethylaminoethyl)imidazole (169) had previously been prepared either by heating the appropriate β -chloroethyl derivative with dimethylamine in a sealed tube (Garforth and Pyman 1935) or by refluxing these reactants in propanol (Huebner et al. 1949; Huebner 1951).



We prepared the required compound in good yield under the fairly mild conditions of reductive methylation using histamine dihydrochloride as the reaction substrate. At the time of writing, Dr. Ham has only yet completed a 60 MHz analysis of the AA'BB' bimethylene region of the dimethylamino compound (169). His preliminary results indicate that $N = 14.7$ and $L = 2$ and is negative, which suggests that the trans conformer (175) predominates in

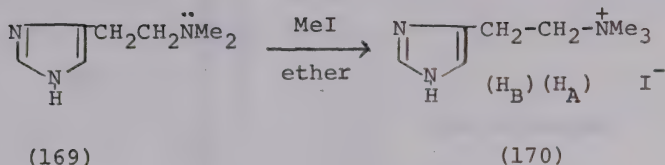


aqueous solution at pH 7 (see discussion in next section, for the significance of N and L values). A 100 MHz analysis is presently being carried out to confirm the 60 MHz results.

(c) Preparation and PMR Examination of 4(5)(Trimethylamino-ethyl)imidazole iodide (170)

The required methiodide was prepared by reaction of the dimethylamino base (169) with methyl iodide in ether

solution. The use of a large excess of methyl iodide was



avoided to prevent possible substitution of the planar and imido ring nitrogen centres. Isolation of the dimethylamino base (169) from its salt was impossible by conventional means owing to its infinite solubility in water (Garforth and Pyman 1935). We therefore obtained an ethereal solution of the required base by trituration of the dihydrochloride with sodium hydroxide pellets in ether containing just a trace of water.

The 100 MHz spectrum of the bimethylene and imidazole ring proton regions of the methiodide in D_2O is shown in Figure 25. The system was again AA'BB' and Dr. Ham carried out computerised iterative calculations using only the low-field H_A multiplet. This avoided further complication by the significant (1.5-2.0 Hz) three-bond $\text{Me}_3\text{N}^+ - \text{C}^{\text{H}} -$ coupling acting on the higher field H_B protons (Culvenor and Ham 1966 and references there cited). The parameters obtained were:

$$\begin{array}{ll}
 \text{N} & = \quad 15.9 \text{ Hz} \\
 \text{L} & = \quad 5.02 \text{ Hz} \\
 \text{M} & = \quad 1.1 \text{ Hz}
 \end{array}$$

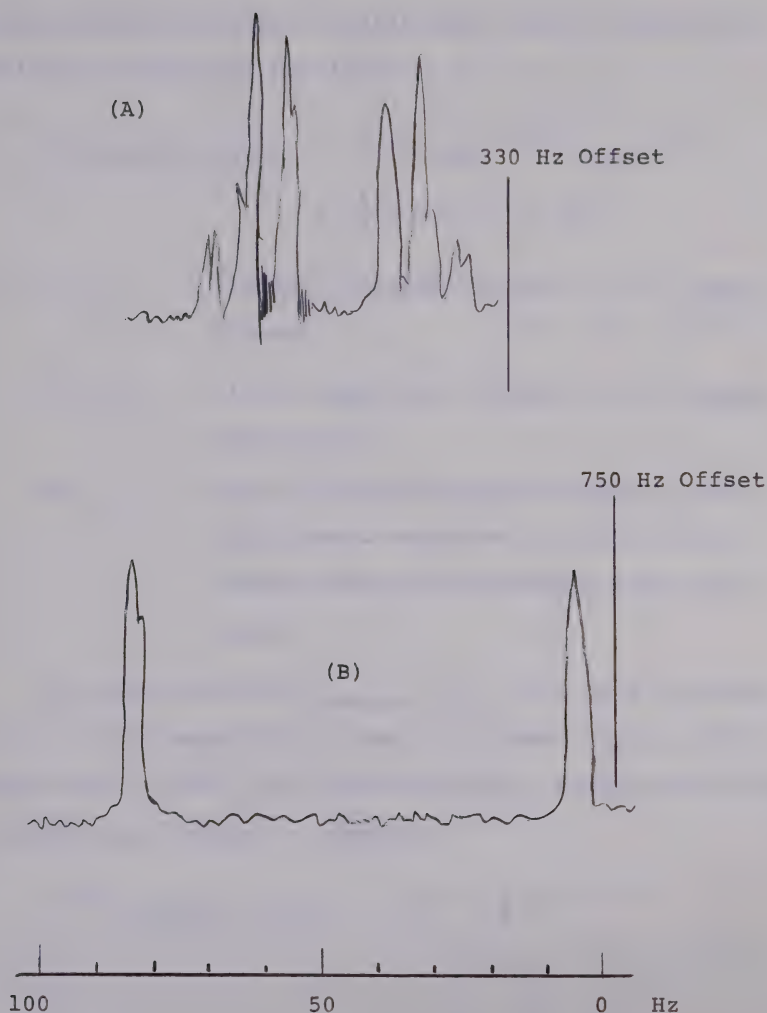


Figure 25. (A) Offset 100 MHz bimethylene region of the quaternary methiodide (170) in D_2O (pH 6.8) relative to external TMS. (B) Offset 100 MHz imidazole ring proton resonance absorptions of the same compound.

Determination of the sign of L was obtained by use of Abraham and Pachlers' relationship (1964) (cf. acetylcholine, Culvenor and Ham 1966):

$$\begin{aligned} J_{\text{average vicinal}}^* &= \frac{1}{3} (J_{\text{trans}} + 2 J_{\text{gauche}}) \\ &= \left(\frac{1}{2} N + \frac{1}{6} L \right)^{\dagger} = \Sigma E \end{aligned}$$

where J_{trans} = vicinal coupling constant of the trans rotamer

J_{gauche} = vicinal coupling constant of the gauche conformers

ΣE = sum of the electronegativities of the substituents attached to the vicinal carbon atoms on the Huggins scale (see below).

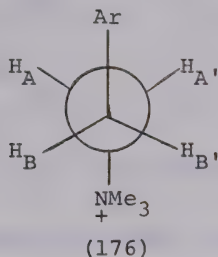
Dr. Ham obtained $J_{\text{average vic.}} = 6.4$ to 6.8 Hz depending on the magnitude of the 'E' values (Huggins 1953) assumed for the NMe_3^+ and imidazole moiety substituents used in Abraham and Pachler's equation.

$$\begin{aligned} \text{But } J_{\text{average vicinal}} &= \frac{1}{2} N + \frac{1}{6} L \\ &= 7.95 + \frac{1}{6} (\pm 5.02) \\ &= 7.95 + (\pm 0.84) \\ \therefore J_{\text{average vicinal}} &= 8.79 \text{ if } L \text{ is } +ve \\ &\text{or } 7.11 \text{ if } L \text{ is } -ve \end{aligned}$$

* This value will be independent of the conformer populations.

† This value is constant (Abraham and Pachler 1964)

The closer proximity of ΣE (6.4 to 6.8) to the J_{average} vicinal value (7.11) calculated from consideration of L being negative strongly suggested that $L = -5.02$ i.e. $J_{AB'} > J_{AB}$ ($L = J_{AB} - J_{AB'}$) with the trans conformer (176) being favoured.



Ar = 4(5)-imidazolyl

In addition J_{AB} and $J_{AB'}$ could be calculated:

$$N = J_{AB} + J_{AB'} = 15.9$$

$$L = J_{AB} - J_{AB'} = -5.02$$

$$\therefore 2 J_{AB} = 10.88$$

$$\text{i.e. } J_{AB} = 5.44$$

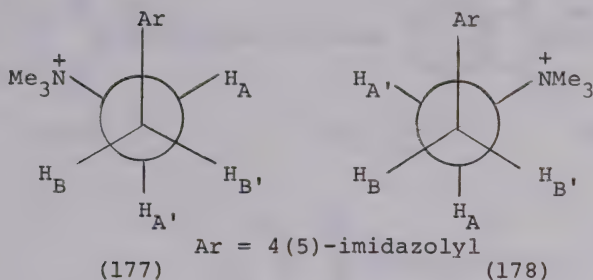
$$\text{and } J_{AB'} = 10.46$$

These time averaged J_{AB} and $J_{AB'}$ parameters were consistent (Karplus theory, see earlier) with the gauche and trans couplings in the preferred trans rotamer (176) i.e. one 'small' (5.44 Hz) and one 'large' (10.46 Hz) value respectively.

If the gauche conformers (177 and 178) had been favoured then J_{AB} would have been about $(10 + 5)/2 = 7.5$ Hz and $J_{AB'} = \text{ca. } 5$ Hz because:

$$J_{AB} = \frac{1}{2} (J_{trans} + J_{gauche})$$

and $J_{AB'} = \frac{1}{2} (J_{gauche} + J_{gauche}) = J_{gauche}$

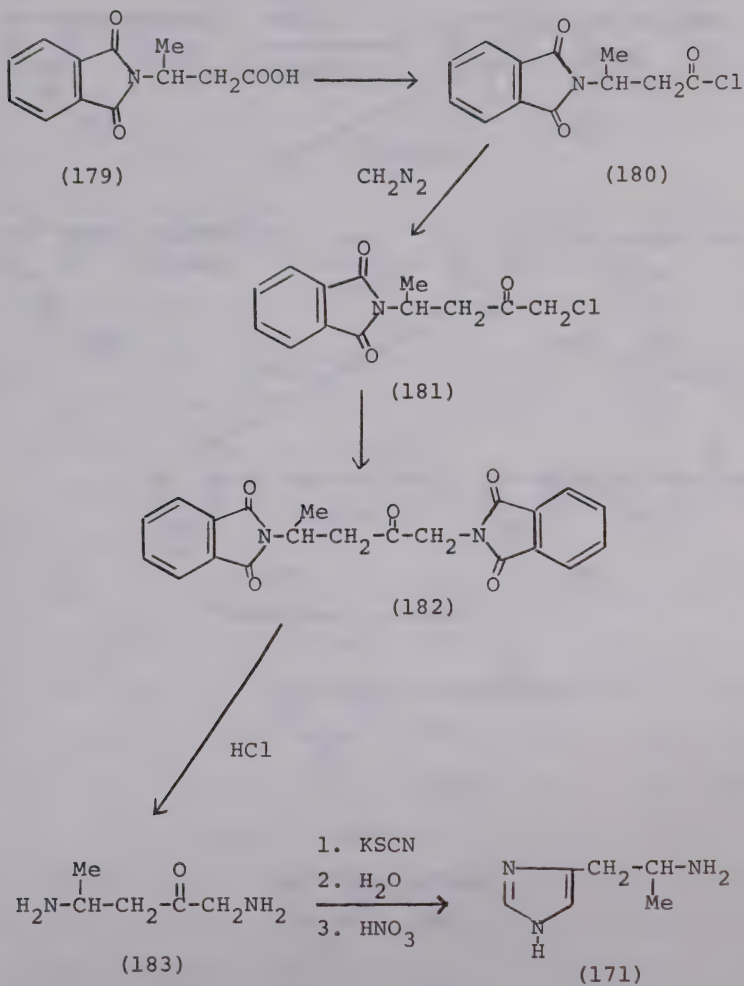


Thus, the observed 'small' and 'large' J_{AB} and $J_{AB'}$ values provided further evidence for the trans methiodide rotamer (176) predominating in aqueous solution as would reasonably be expected from qualitative energy considerations.

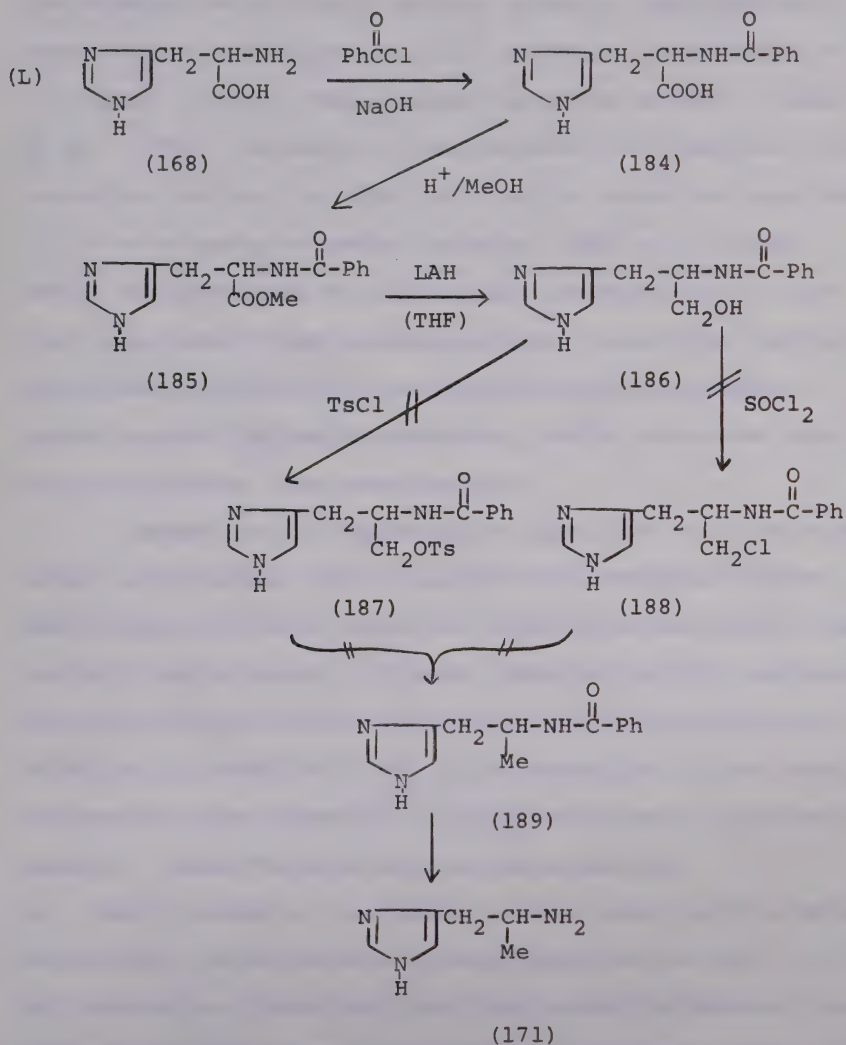
(d) Preparation and PMR Examination of α -Methylhistamine

The preparation of α -methylhistamine has been described once in the literature by Alles and his group in 1957 (see flow sheet below). These workers commenced their synthetic route by conversion of 2-phthalimidobutyric acid (179) to the acid chloride (180); the latter was treated with diazomethane to yield 1-chloro-4-phthalimidopentane-2-one (181) which was then reacted with potassium phthalimide in dimethyl formamide to form 1,4-diphthalimidopentane-2-one (182). Hydrolysis then yielded 1,4-diaminopentan-2-one (183) which was converted to α -methylhistamine (171) by Pyman's (1911)

classic synthesis for the preparation of imidazoles from aminoketones.



We did not utilise the literature preparation but instead gave thought to other possible routes arising from

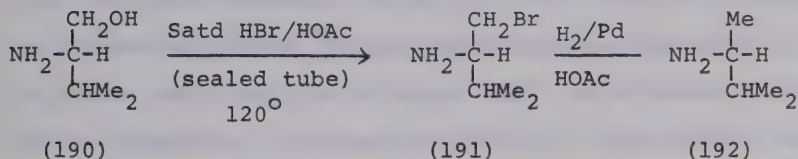


more readily accessible starting materials. In the event we chose L-histidine (168) as the precursor and pursued the alternative synthetic pathway shown on the previous page; the amino acid was initially converted to N-benzoyl-histidinol (186) by three stages using the method of Adams et al. (1955); initially it was intended to O-tosylate the histidinol derivative (186) and then to reduce the tosylate (187) to N-benzoyl α -methylhistamine (189) which might easily be hydrolysed to the required product (171). However, all three O-tosylation reactions failed when the substrate was treated with p-toluene sulphonyl chloride in either aqueous potassium carbonate, sodium hydroxide solution or pyridine (see experimental).

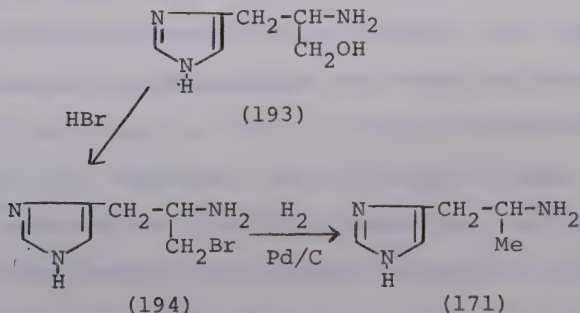
Conversion of N-benzoylhystidinol (186) to the chloromethyl intermediate (188) (see previous synthetic scheme) which might similarly yield the required Me derivative also failed. Use of thionyl chloride (neat or in CHCl_3 solution), phosphorus oxychloride or phosphorus pentachloride as the chlorinating agents all lead to decomposition of the reaction mixture with the formation of intractable tars (see experimental). These failures may have been due to:

(a) Acid cleavage of the amide bond to form the free amine which could yield unstable N-oxide products, or (b) $\text{O} \rightarrow \text{N}$ acyl migration (Fodor and Kiss 1950) occurring between the vicinal $-\text{CH}-\text{NH}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{Ph}$ and $-\text{CH}_2\text{OH}$ groups which would again lead to an unprotected and oxidatively vulnerable amino grouping.

We therefore focused our attention on further possible synthetic routes to α -methylhistamine (171); while searching a review by Klyne and Mills (1954) concerned with absolute stereochemical correlations, an interesting reference (Barrow and Ferguson 1935) was noted. This concerned the conversion of the aminoalcohol (190) via the bromo compound (191) to α -methylisobutylamine (192). The aminoalcohol (190) may be regarded as an analogue of



histidinol (193) as both compounds contain the $-\text{CH}(\text{NH}_2)\text{CH}_2\text{OH}$ unit. It was therefore decided to use Barrow and Ferguson's method to attempt to prepare the appropriate bromo derivative (194) of histidinol which might then be reduced to α -methylhistamine (171).

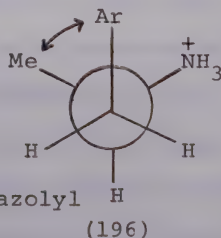
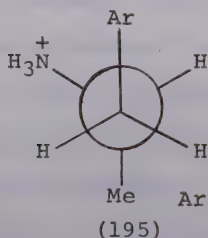


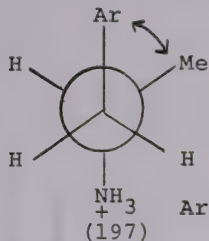
Initially, a sample of histidinol dihydrochloride (193) was prepared by acidic hydrolysis of the N-benzoyl derivative (186) according to Adams et al. (1955). Treatment of the former with a 32% solution of hydrobromic acid in acetic acid at atmospheric pressure under reflux conditions yielded only unchanged starting material. It was therefore decided to simulate the sealed tube conditions used by Barrow and Ferguson for their preparation of α -bromomethylisobutylamine (191); a sample of histidinol in the free base form was treated with the brominating agent in a pressure bottle (Fisher Scientific) at 100-120° for 35 hr but this reaction afforded only the dihydrobromide of the substrate. A fresh bottle of 32% hydrobromic acid had been used for this experiment and the straw colour of this reagent was noticeably lighter than that of an older sample to hand. A repeat experiment using the older brominating reagent (red-brown in colour) under the same conditions as above was successful with the required bromo derivative (194) being obtained in good yield. It is therefore possible that traces of free bromine catalyse this reaction.

Attempts to hydrogenolyse the bromo compound (194) using Pd/C in ethanol or PtO₂ in ethanol or methanol all failed with only unchanged starting material being recovered. However, reduction to α -methylhistamine was successful (PMR evidence) when Barrow and Fergusons' reaction conditions were employed; this involved use of a polar 10% aqueous

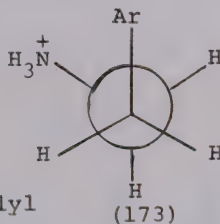
acetic acid solvent system containing 2% sodium acetate and the Pd/C catalyst.

Unfortunately this reaction yielded a sample of α -methylhistamine contaminated with sodium acetate solid (see experimental) and several recrystallisation attempts failed to remove the inorganic contaminant. Purification of the product by release of the free base and extraction into organic solvents also failed (even after saturation of the aqueous phase with sodium chloride) owing to the infinite solubility of the base in water. However, α -methylhistamine was finally isolated as the dipicrate derivative which was formed by addition of picric acid to the basified layer. The latter derivative melted about 20° lower than the dipicrate monohydrate obtained by Alles and others (1957). However, a subsequent IR spectrum and micro-analysis revealed that our compound was the anhydrous dipicrate. A PMR spectrum of the pure derivative was not feasible owing to its very high molecular weight and insolubility in D_2O and thus the conformational equilibrium of α -methylhistamine could not be studied and compared to histamine or its dimethylamino (169) and quaternary methiodide (170) derivatives.





Ar = 4(5)-imidazolyl



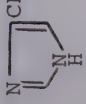
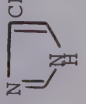
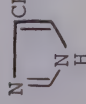
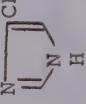
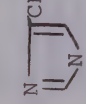
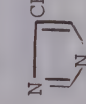
This was unfortunate as the gauche rotamer (195) of α -methylhistamine might well be favoured over the other possible trans (197) and gauche (196) forms in contrast to the previously discussed Me analogues of histamine; this deduction is derived from the fact that the similar gauche conformer of histamine (173) is of almost equal energy to its corresponding trans form (Kier 1968, and present PMR evidence) in spite of the closer proximity of the Ar and NH_2^+ groups in the former. It therefore appears that some favourable form of electronic interaction between the adjacent Ar and NH_2^+ groups in the gauche form (173) of histamine overcomes any repulsive steric energies which might be present in the molecule.

In the case of α -methylhistamine it was therefore considered that the Ar \leftrightarrow Me steric clashing in the gauche (196) and trans (197) rotamers might be of a more serious nature than in the gauche form (195) which may result in the latter conformer being energetically more stable.

However, the 60 MHz spectra of the crude α -methylhistamine product (contaminated with sodium acetate) clearly established the presence of a secondary Me group (doublet in high field region); the details of this spectrum and those of histamine, its methylated analogues and all the imidazole intermediates mentioned in this Chapter were

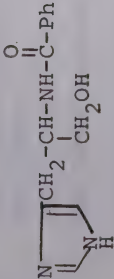
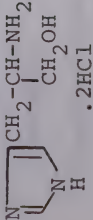
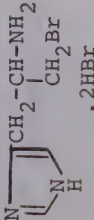
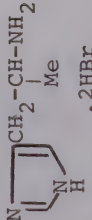
TABLE XX

60 MHz PMR CHARACTERISTICS OF SOME IMIDAZOLE DERIVATIVES

Structure	Compound Number in text	Solvent	Chemical Shifts ^a		
			Imidazole ring protons C-2 ^b	Others	
 <chem>Nc1c[nH]cn1</chem> · 2HCl	(1)	D ₂ O	527	451	<u>CH₂CH₂N</u> 200 ^d
 <chem>CN(C)C1=CN=CNC1</chem> · 2HCl	(169)	D ₂ O	524	450	<u>CH₂CH₂N</u> 207 ^d <u>NMe₂</u> 181 ^e
 <chem>CN(C)C1=CN=CNC1</chem> I ⁻	(170)	D ₂ O	446 ^c	426	<u>CH₂CH₂N</u> 216 ^d + <u>NMe₃</u> 192 ^e
 <chem>OCC1=CN=CNC1</chem> · HCl · H ₂ O	(168)	D ₂ O ^f	520	447	<u>CH-N</u> 226 ^d <u>CH₂</u> 191 ^g (J7)
 <chem>O=C(Cc1c[nH]cn1)Cc2ccccc2</chem>	(184)	DMSO-d ₆	- _h	417	<u>NH-C</u> 521 ^j (J8) <u>CH-N</u> 281 ^d <u>CH₂</u> 187 ^j (J7) <u>CHN</u> 282 ^d
 <chem>COC(=O)c1c[nH]cn1CC(=O)Cc2ccccc2</chem>	(185)	DMSO-d ₆	- _h	416	<u>COOMe</u> 218.5 ^e <u>CH₂</u> 185 ^j (J7)

Continued

TABLE XX (Continued)

Structure	Compound Number in text	Solvent	Chemical Shifts ^a		
			Imidazole ring protons C-2 ^b	C-(4,5) ^c	Others
	(186)	DMSO-d ₆	- ^h	407	$\overline{\text{CHN}}$ 250 ^d $\overline{\text{CH}_2\text{OH}}$ 206 ^j (J7) $\overline{\text{CH}_2}$ 169 ^j (J7)
	(193)	D ₂ O	525.5	451	$\overline{\text{CH}}$ and $\overline{\text{CH}_2\text{OH}}$ c230 ^k $\overline{\text{CH}_2}$ 193 ^g (J6.5)
	(194)	D ₂ O	522 ^c	449	$\overline{\text{CH}}$ and $\overline{\text{CH}_2\text{Br}}$ 200-250 ^l $\overline{\text{CH}_2}$ 198 ^h (J7)
	(171)	D ₂ O ^m	506 ^c	443	$\overline{\text{CHN}}$ 224 ^d $\overline{\text{CH}_2}$ 185 ^j (J7) $\overline{\text{CH-Me}}$ 83 ^j (J7)

^a Chemical shifts relative to DDS for D₂O or TMS for DMSO-d₆ solutions; coupling constants (J) in Hz.

^b Doublet (J 1.5).

^c Broad singlet.

^d Centre of multiplet.

Continued

TABLE XX (Continued)

- e Singlet.
- f This spectrum is fully discussed by Pachler (1963) who classified it as of the AX_2 type.
- g Deformed doublet.
- h Submerged under aryl multiplet.
- j Doublet.
- k Centre of overlapping methane and $\underline{CH_2}OH$ signals.
- l Complex of overlapping methine and $\underline{CH_2}Br$ signals.
- m Contaminated with sodium acetate.

recorded at 60 MHz for reference purposes and are shown in Table XX.

Finally, it should be noted that the α -methylhistamine dipicrate derivative has been submitted for antihistaminic evaluation but no results are yet to hand; this was done because it is well known that introduction of small alkyl groups may radically alter the pharmacological properties of an agonist. For example, α -methylacetylcholine has enhanced nicotinic but reduced muscarinic properties compared to acetylcholine. This trend is reversed in the β -methyl analogue with the muscarinic activity being increased and the nicotinic reduced (Simonart 1932). A further example is shown by the conversion of morphine (N-Me agonist) to nalorphine (N-CH₂-CH=CH₂ analogue) which results in the formation of a potent analgesic antagonist.

(ii) Pharmacological Discussion of Histamine and its Side-chain Methyl Analogues

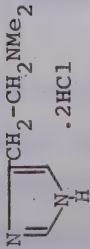
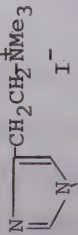
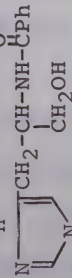
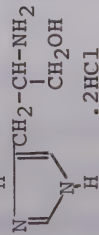
(a) Antihistaminic Data

The dimethylamino (169) and quaternary methiodide (170) derivatives of histamine together with the two intermediates isolated during the synthesis of α -methylhistamine were routinely evaluated for antihistaminic potency. The pharmacological data obtained are given in Table XXI; none of the compounds tested showed any appreciable activity.

TABLE XXI

INHIBITION OF HISTAMINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA-PIG ILEUM BY SOME

IMIDAZOLE DERIVATIVES

Structure	Compound Number in text	Conc. μg/ml	Percentage inhibition at time (in min.)					
			3	6	9	12	15	18
	(169)	1.0	100	84	13	0	-	-
	(170)	1.0	69	0	-	-	-	-
	(186)	10.0	25	8	0	-	-	-
	(193)	10.0	52	0	-	-	-	-
Mepyramine standard	(37)	0.001	94	77	47	31	15	0
"	"	"	100	95	73	57	0	-
"	"	"	50	29	18	0	-	-
"	"	"	69	52	38	10	0	-

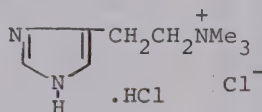
N.B. In this table, a dash denotes discontinuation of experimental observation.

(b) Agonist Activities

The histamine-like agonist activities of several appropriate Me analogues were obtained from the literature and are given in Table XXII. Included are the monomethyl derivative (198) and the quaternary methchloride hydrochloride (199) (comparable to the methiodide (170) previously described).



(198)





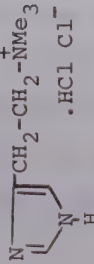

(199)

The data available is not extensive and only in one case has two of the histamine derivatives been examined in the same laboratory. This sparsity of pharmacological data together with the lack of knowledge about how distribution factors affect the potency of histamine agonists do not therefore allow any firm conclusions to be drawn about the conformational preference, if any of the H₁ and H₂ histamine receptors.

Under physiological conditions, it has already been shown that histamine has no preferred conformation. This means that statistically there is 1/3 of the trans and 2/3 of the gauche conformers present at any given moment. It therefore might be tacitly assumed that there is a greater chance of the gauche conformers associating at the receptor.

TABLE XXII

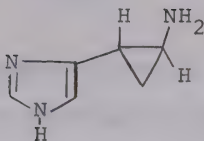
HISTAMINE-LIKE PROPERTIES OF SOME SIDECHAIN METHYL ANALOGUES OF HISTAMINE

Structure	Compound Number in text.	Relative activity of histamine = 1		
		Guinea-pig ileum contraction	Blood pressure fall in cats or dogs	Stimulation of gastric secre- tion in cats or dogs
	(198)	1.0 ^a , 2.0 ^b , 2.5 ^c	0.5 ^a	2.5 - 3.0 ^d
	(169)	0.80 ^b	0.20 ^a	2 - 3 ^d
	(199)	0 ^a	0 ^a	no data
	(171)	0.01 ^e , 0.004 ^g	0.01 ^e	'active', ^f 0.003 ^g

^a Vartiainen, 1935.^b Huebner et al. 1949.^c Schild, 1947.^d Alphin and Lin, 1960.^e Alles et al. 1943.^f Grossman et al. 1952.^g Burger et al., 1970.

However, the energies of the trans and gauche forms are very similar (Kier 1968, molecular orbital calculations and our own PMR evidence) so that transfer from the gauche to trans conformation might easily occur at the receptor. In contrast, crystalline histamine (acid phosphate) exists entirely in the trans conformation (Palenik and Veidis 1969; Palenik et al 1969; X-ray evidence).

Thus it is very difficult to come to any conclusion as to whether or not there is a preferred 'active' histamine conformation; considerably more comparative pharmacological and conformational data on histamine analogues of greater molecular rigidity are required before any firm theories may be drawn. However, it is of interest to note that the gastric secretory activities of the mono- (198) and dimethyl (169) derivatives of histamine are distinctly more potent than histamine itself. The dimethyl analogue has been shown to exist predominantly in the trans conformation and the monomethyl compound might also be expected to exist to a greater extent in this conformation. From this evidence it therefore appears that the trans conformer may be preferentially taken up by the H_2 receptor which is held to be responsible for the gastric secretory effects of histamine. However, a recent report (Burger et al. 1970) concerning 2-(4-imidazolyl)cyclopropylamine (200) contradicts such speculation; the gastric secretory (0.016) and guinea-pig ileum (0.008) activities of this

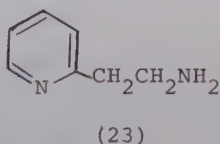
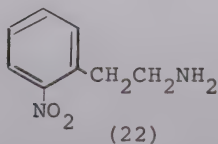


(200)

compound relative to histamine (activity =1) were found to be extremely weak. Most significantly, this molecule is rigid and the imidazolyl and amino functions are trans to one another and separated by a distance which will be very close to that obtaining in the trans conformer of histamine. It is interesting to note that Kier's postulate (1968) and our own structure:activity work on the model aminoalkene antihistaminics (see Chapters 3 and 4) have indicated that the trans conformer is interacting at the H_1 receptor.

(iii) Attempts to Introduce the Imidazole Nucleus Into an Antihistaminic Structure

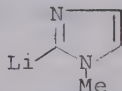
It has previously been noted (see Chapter 2) that the o-nitrophenyl and 2-pyridyl analogues (22 and 23) of



histamine have negligible agonist effects on the guinea-pig ileum (Jones 1966) and yet the phenyl and 2-pyridyl moieties are common aromatic features of many potent antihistamines.

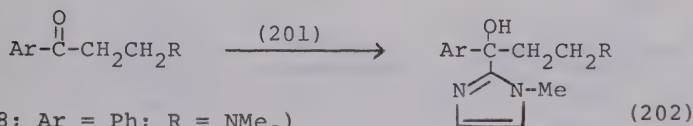
In addition, there appeared to be no reference in the literature to any antihistamines containing the imidazole nucleus and it therefore seemed of interest to attempt to introduce this heterocycle into a molecular structure having potential antihistaminic properties.

In this regard it was decided to investigate use of the ethereal 2-lithio-1-methylimidazole (201) complex previously described by two sources (Alley and Shirley 1957; Roe 1963). It was intended to treat a Mannich




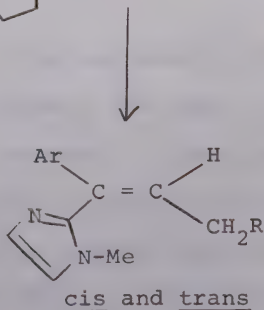
(201)

ketone (38 or 103) with the latter reagent to produce the corresponding carbinol (202) whose dehydration might yield



(38; Ar = Ph; R = NMe₂)

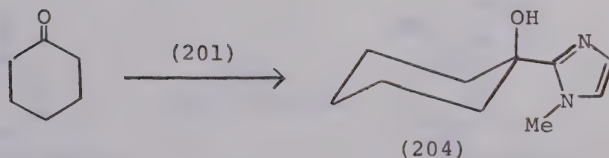
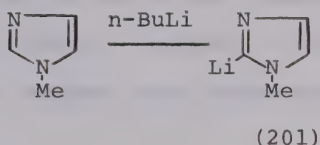
(103; Ar = p-Me-C₆H₄; R = )



(203)

cis and trans aminopropene isomers (203) possessing 'active' antihistaminic structures containing the imidazole nucleus.

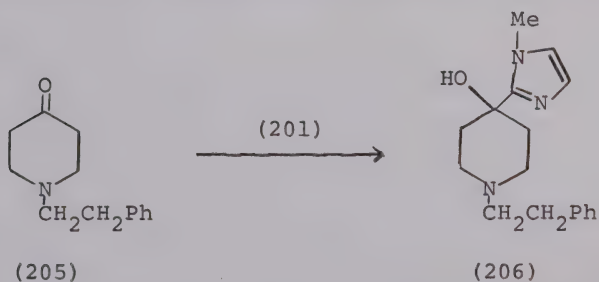
Initially, effective preparation of the organo-lithium reagent (201) was investigated; both Roe (1963) and Alley and Shirley (1957) had synthesised the complex by treatment of 1-methylimidazole with n-BuLi at room temperature for three hours. We prepared the complex according to the literature conditions and repeated Roe's reaction of this reagent with cyclohexanone.



Only a 4% yield of the imidazolyl product (204) was thus obtained (Roe claimed a 56% yield in a very much smaller scale reaction). However a classic review (Gilman and Morton 1954) on metalation reactions quoted quite unequivocally that 'metalation involves boiling under reflux in ether solution of a substance to be metalated together with an excess of n-butyl lithium from four to twenty four

hours'; therefore we reprepared the lithio-imidazole reagent under reflux conditions and subsequent treatment with cyclohexanone produced the much improved yield of 52% of the expected product (204).

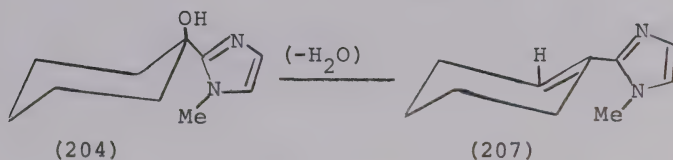
Having established suitable conditions for effective preparation of the organolithium reagent attempts were then made to react the latter with two different Mannich ketones (38 and 103). No detectable reaction occurred and only unchanged ketone was isolated in either case. The experimental failure of these reactions was thought possibly to be due to the presence of a basic centre in the substrates. Indeed, a further reaction of the organolithium reagent with N-phenethyl-4-piperidone



(205) (an analogue of cyclohexanone containing a basic group) afforded only an 11% yield of the tertiary alcohol product (206). Thus it did appear that reaction of the imidazole-lithium complex is inhibited by the presence of a basic group in a ketonic substrate. Hence, the imidazole nucleus could not be introduced into an antihistaminic

structure by use of the reagent.

Furthermore, attempts to dehydrate the model imidazole carbinol (204) (using an acetic-hydrochloric acid



mixture or sulphuric acid) to form an alkenic structure (207) of potential antihistaminic interest also failed (see experimental).

CHAPTER 8

EXPERIMENTAL

Notes on the Experimental Data

All Melting Points are uncorrected and were determined using a Thomas Hoover Capillary melting point apparatus. Infrared Spectra were recorded on a Beckmann Infrared Spectrophotometer Model 10 (solids as Nujol mulls and liquids as thin films unless otherwise specified). UV Spectra were obtained by use of a Beckmann DK-2 Recording Spectrophotometer.

PMR Spectra were determined at 60 MHz on a Varian Associates Model A-60D spectrometer at the normal operating temperature of 39°; 100 MHz spectra were recorded on a Varian HA-100 instrument. In both instances, the chemical shifts were recorded in Hz relative to TMS or DSS as internal standards.

Elemental Analyses were carried out by Drs. G. Weiler and F.B. Strauss, Microanalytical Laboratory, Oxford, England and by the microanalytical laboratories of the Department of Chemistry and the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta.

Bases, unless otherwise indicated, were recovered from their acidic solutions by making alkaline with ammonia. The liberated bases were extracted with ether, dried over anhydrous sodium sulphate, filtered and the extracts evaporated to dryness.

All the commercial chemicals were used without further purification unless otherwise specified. The anhydrous ether reagent (Ex Fisher Chemicals) was used directly for the Grignard and organolithium reactions and it was found unnecessary to stand this solvent over sodium wire.

EXPERIMENTAL WORK RELEVANT TO CHAPTER 3, SECTIONS (ii) TO
(vii) GENERAL STUDIES ON 4-AMINO BUTENES

Synthesis of the 1,2-Diaryl Mannich Ketones

All the ketones described below exhibited strong IR carbonyl absorption bands in the $1700-1650\text{ cm}^{-1}$ region.

3-Dimethylamino-1-phenylpropan-1-one (38)

Acetophenone (40 g; 0.33 M), dimethylammonium chloride (35 g; 0.43 M) and paraformaldehyde (13 g; 0.43 M) in ethanol (50 ml) containing 1 ml of HCl, were heated under reflux for 4 hr, cooled and diluted with ether until the solution was close to the coalescence point. After storage at 0° for several hours, the colourless, crystalline Mannich ketone (38) hydrochloride (46.3 g; 66%) separated, m.p. $153-154^{\circ}$ (Maxwell, 1943, gave m.p. $155-156^{\circ}$).

3-(1-Piperidino)-1-phenylpropan-1-one (41)

Prepared as above using acetophenone (60 g; 0.5 M), piperidine (42.6; 0.5 M) and paraformaldehyde (19.8 g; 0.65 M). The organic base was carefully acidified to litmus with concentrated HCl, cooling the solution in an ice-bath, before being treated with the other reactants. The hydrochloride product (41) separated as colourless needles (66.1 g; 52%), m.p. $190-191^{\circ}$ (EtOH/ether) (Mannich and Lammering, 1922, gave m.p. $192-193^{\circ}$).

1-Phenyl-3-(1-pyrrolidino)propan-1-one (42)

Prepared as above using acetophenone (60 g; 0.5 M), paraformaldehyde (19.8 g; 0.65 M) and acidified pyrrolidine (35.6 g; 0.5 M) to yield the crude hydrochloride product (42) (99.7 g; 83%), m.p. 162-163° (EtOH/ether) (Adamson et al., 1950, gave m.p. 162-164°).

3-Dimethylamino-1-o-tolylpropan-1-one (61)

o-Methylacetophenone (49.2 g; 0.37 M), dimethylammonium chloride (37.3 g; 0.46 M) and paraformaldehyde (15.0 g; 0.5 M) were treated as before to give the hydrochloride product (61) (62.1 g; 74%), m.p. 154° (EtOH/ether) (Burckhalter and Johnson, 1951, gave m.p. 156°).

Found: C, 62.91; H, 7.91; N, 6.12. $C_{12}H_{17}NO.HCl$ requires: C, 63.28; H, 7.97; N, 6.15%.

Preparation of the 4-Amino-1,2-Diarylbutan-2-ols

The hydrochlorides of all the carbinols described below showed characteristic hydroxyl absorptions in the 3300-3250 cm^{-1} region of their IR spectra.

General Preparative Method

The appropriate Mannich ketone in the free base form (1 mole) was treated with the Grignard reagent prepared from benzyl chloride (2 mole) and magnesium (2.2 g atom) in anhydrous ether at reflux temperature for 3 hr. The reaction

mixture was then decomposed with crushed ice and ammonium chloride. The ether layer was separated, dried (Na_2SO_4) and evaporated to dryness to yield the crude basic product as a yellow oil. The latter was dissolved in ethanol and acidified to litmus with a stream of dry HCl gas, cooling the reaction flask in an ice-bath (to prevent possible dehydration). Addition of anhydrous ether to the solution and storage at 0° yielded the crystalline hydrochloride product.

In the above manner, the following carbinols were isolated:

4-Dimethylamino-1,2-diphenylbutan-2-ol (29a) hydrochloride, yield 41%, m.p. $157-158^\circ$ (EtOH/ether) (Pohland and Sullivan, 1953, gave m.p. $156-157^\circ$).

1,2-Diphenyl-4(1-piperidino)butan-2-ol (26c; R = H) hydrochloride, yield 42%, m.p. $233-234^\circ$ (EtOH/ether) (Pohland and Sullivan, 1953, gave m.p. $232-233^\circ$).

1,2-Diphenyl-4(1-pyrrolidino)butan-2-ol (39) hydrochloride, yield 42%, m.p. 163° (EtOH/ether).

Found: C, 72.03; H, 7.80; N, 4.22. $\text{C}_{20}\text{H}_{25}\text{NO} \cdot \text{HCl}$ requires: C, 72.38; H, 7.90; N, 4.22%.

1-p-Chlorophenyl-2-phenyl-4(1-pyrrolidino)butan-2-ol (40) hydrochloride, yield 71%, m.p. 190° (EtOH/ether). (Eli Lilly Co., Patent 1953a, gave m.p. $185-187^\circ$).

Found: C, 65.82; H, 7.03; N, 3.82. $C_{20}H_{24}ClNO.HCl$ requires: C, 65.57; H, 6.88; N, 3.82%.

4-Dimethylamino-1-phenyl-2-*o*-tolylbutan-2-ol (62) hydrochloride, yield 65%, m.p. 169° (EtOH/ether) (Pohland and Sullivan, 1953, gave m.p. $169-170^{\circ}$).

Found: C, 71.41; H, 8.57; N, 4.47. $C_{19}H_{25}NO.HCl$ requires: C, 71.34; H, 8.19; N, 4.38%.

Acid-Catalysed Elimination of 4-Amino-1,2-diarylbutan-2-ols

General Method of Casy and Pocha (1967)

The aminobutan-2-ol hydrochloride (10 to 20 g) was dissolved in a mixture of hydrochloric (75 ml) and acetic acids (175 ml) and heated under reflux for 4 hr. The cooled solution was made alkaline with strong, aqueous ammonia and the base extracted into ether. The dried (Na_2SO_4) extracts were evaporated down to dryness and a sample of the total base examined by PMR spectroscopy (see Chapter 3). The product was then acidified to litmus with ethanolic hydrogen chloride or bromide and small amounts of ether were successively added to the solution over a period of several weeks. Continuous standing at 0° led to the isolation of a large number of crystalline hydrohalide crops. Numerous recrystallisations from EtOH/ether were carried out and PMR spectra of selected crops were run to determine their isomeric compositions. In this manner, certain pure samples or enriched mixtures of the various aminobutene isomer products with

characteristic PMR parameters (see Tables III and V) were isolated.

By the above method, the following carbinols were dehydrated:

4-Dimethylamino-1,2-diphenylbutan-2-ol (29a) hydrochloride (20 g) gave several diversely mixed crops of the various aminobutene isomers until eventually a crude mixture of the required cis (H/Ph) but-2-ene (33) hydrobromide, (2.30 g), and a trace amount of the cis but-1-ene (30) was obtained (PMR evidence, see p. 36). Several recrystallisations of this crop from EtOH/ether finally yielded the pure cis (H/Ph) but-2-ene (33) hydrobromide as colourless needles, m.p. 179-180°.

Found: C, 64.71; H, 6.57; N, 3.93. $C_{18}H_{21}N.HBr$ requires: C, 65.07; H, 6.67; N, 4.22%.

Also isolated was a mixture, (3.13 g), m.p. 127-130°, consisting mainly of the cis and trans but-1-ene (30 and 31) hydrobromides together with a trace amount of the cis (H/Ph)-but-2-ene (33) salt (PMR evidence). A sample of this mixture was subsequently evaluated for antihistaminic activity (see Table IV).

Dehydration of 1,2-diphenyl-4-(1-piperidino)butan-2-ol (26c; R = H) hydrochloride, (10 g), led to the isolation of the following aminobutene isomers in the order given below:

cis (H/Ph) but-2-ene (41) hydrochloride, (1.54 g), m.p. 248-249° (EtOH/ether).

Found: C, 76.68; H, 8.12; N, 4.23. $C_{21}H_{25}N.HCl$ requires: C, 76.91; H, 8.00; N, 4.27%.

trans but-1-ene (44) hydrochloride, (1.42 g), m.p. 195° (EtOH/ether).

Found: C, 76.71; H, 8.04%.

cis but-1-ene (43) hydrochloride, (0.67 g), m.p., 160-161° (EtOH/ether).

Found: C, 76.97; H, 7.98%.

Dehydration of 1,2-diphenyl-4(1-pyrrolidino)-butan-2-ol (39) hydrochloride, (13.5 g), produced the following aminobutene isomers in the order given below:

cis (H/Ph) but-2-ene (47) hydrochloride, (0.77 g), m.p. 198° (EtOH/ether).

Found: C, 76.58; H, 7.48. $C_{20}H_{23}N.HCl$ requires: C, 76.30; H, 7.68%.

trans but-1-ene (50) hydrochloride, (1.53 g), m.p. 160-162° (EtOH/ether).

Found: C, 76.28; H, 7.83%.

Conversion of the mother liquor to a hydrobromide mixture only led to the isolation of more trans but-1-ene (50) as the hydrobromide (see Table VI), (0.56 g), m.p.

141-142° (PMR spectrum in CDCl_3 identical to that of the hydrochloride of this isomer - see Table V).

Dehydration of 1-p-chlorophenyl-2-phenyl-4-(1-pyrrolidino)butan-2-ol (40) hydrochloride, (12.0 g), led to the isolation of the following aminobutene isomers in the order given below:

cis (H/Ph) but-2-ene (51) hydrochloride, (1.73 g), m.p. 227-228° (this isomer is 'Pyronil' hydrochloride, see p. 51).

Found: C, 69.06; H, 6.59; N, 4.16. $\text{C}_{20}\text{H}_{22}\text{ClN} \cdot \text{HCl}$ requires: C, 68.96; H, 6.66; N, 4.02%.

trans but-1-ene (54) hydrobromide, (2.01 g), m.p. 191° (EtOH/ether).

Found: C, 61.16; H, 6.07; N, 3.69. $\text{C}_{20}\text{H}_{22}\text{N} \cdot \text{HBr}$ requires: C, 61.15; H, 5.90; N, 3.57%.

cis but-1-ene (53) hydrobromide, (1.30 g), m.p. 184-185° (EtOH/ether).

Found: C, 61.36; H, 6.16; N, 3.29%.

trans but-2-ene (52) hydrobromide, (0.44 g), m.p. 152-153°

Found: C, 60.96; H, 6.03; N, 3.69%.

Dehydration of 4-dimethylamino-1-phenyl-2-o-tolylbutan-2-ol (62) hydrochloride, (15.0 g), led to the isolation of the following products in the order given below:

cis (H/o-tolyl) but-2-ene (63) hydrochloride, (1.33 g) m.p. 188-190° (EtOH/ether).

Found: C, 75.63; H, 7.89; N, 4.54. $C_{19}H_{23}N.HCl$ requires: C, 75.58; H, 8.01; N, 4.64%.

cis but-1-ene (65) hydrochloride, (1.66 g), m.p. 172° (EtOH/ether).

Found: C, 75.30; H, 7.99; N, 4.40%.

trans but-1-ene (66) hydrochloride, (1.39 g), m.p. 176-178° (EtOH/ether).

Found: C, 75.56; H, 8.05; N, 4.41%.

Attempt to prepare the ethylene chlorhydrin quaternary derivative of the cis (H/Ph)₄(1-piperidino)but-2-ene (41)

The free base was isolated from the cis (H/Ph) but-2-ene (41) hydrochloride (0.13 g) and dissolved in anhydrous benzene (25 ml). The mixture was refluxed for 66 hr after which the solution was concentrated down to a small volume and some ether was added. Standing at 0° and repeated scratching would only afford an intractable gum.

Preparation of the quaternary methiodide derivative (46)
of the *cis* (H/Ph)₄(1-piperidino)but-2-ene (41)

The free base isolated from the *cis* (H/Ph) but-2-ene (41) hydrochloride (0.66 g) was dissolved in A.R. acetone (25 ml) and methyl iodide (0.2 ml) was added dropwise. Anhydrous ether was added to the solution until close to coalescence point and on standing at 0° lustrous platelets of the methiodide product (46) (0.44 g) separated, m.p. 163-164° (dec.).

Found: C, 61.18; H, 6.78. C₂₂H₂₈I^N requires:
C, 60.95; H, 6.51%.

The product had the following PMR characteristics in CDCl₃ (TMS) at 60 MHz: =C-H, triplet, 358 Hz (J₈); -CH₂-N⁺, doublet, 275 Hz (J₈); -CH₂Ph, broad singlet, 252 Hz; N⁺-Me, singlet, 196 Hz.

Preparation of the quaternary methiodide derivative (55)
of 'Pyronil' (51)

This compound was prepared as described above using free base isolated from 'Pyronil' (51) hydrochloride (0.61 g). The product consisted of colourless needles (0.35 g), m.p. 117°.

Found: C, 55.62; H, 5.65. C₂₁H₂₅Cl^IN requires:
C, 55.56; H, 5.55%.

The product had the following PMR parameters in CDCl₃ (TMS) at 60 MHz: =C-H, triplet, 359 Hz (J₈); -CH₂-N⁺, doublet

279 Hz (J8); $-\underline{\text{CH}}_2\text{Ph}$, broad singlet, 250 Hz; $-\text{N}^+\text{Me}$, singlet, 196 Hz.

Catalytic hydrogenation of Pyronil hydrochloride (51) to form the corresponding aminobutane (60)

A mixture of Pyronil hydrochloride (0.35 g), 10% palladized charcoal (0.2 g) and ethanol (100 ml) was stirred with hydrogen at atmospheric pressure until gas absorption ceased (4 hr required). The product was filtered through kieselguhr, the filtrate evaporated and the residue recrystallised from an acetone/ether/hexane solvent system to yield 1-p-chlorophenyl-2-phenyl-4(1-pyrrolidino)butane (60) hydrochloride, (0.15 g), m.p. 158° .

A PMR spectrum of the product in CDCl_3 showed the complete absence of any vinylic signals which indicated that reduction was complete. When the product was dried at 60° under reduced pressure in preparation for micro-analysis its colour was observed to turn from white to pink which indicated some decomposition of the compound.

Found: C, 75.09; H, 8.17. $\text{C}_{20}\text{H}_{24}\text{ClN} \cdot \text{HCl}$ requires: C, 68.59; H, 7.19%.

The analysis is unsatisfactory, hence the material is impure.

EXPERIMENTAL WORK RELEVANT TO CHAPTER 3, SECTION (viii)
THE ROLE OF AROMATIC GROUPS IN CIS (H/Ph) 1,2-DIARYL-
BUTENES

(a) Replacement of the Benzyl Ring by the Cyclohexyl and
2-Pyridyl Moieties

Preparation of 4-Dimethylamino-1-cyclohexyl-2-phenylbutan-2-
ol (67)

The Mannich ketone (38) free base which had been isolated from the hydrochloride salt (19.2 g; 0.09 M) was treated with a solution of cyclohexylmethylmagnesium bromide prepared from cyclohexylmethyl bromide (17.7 g; 0.01 M) (Ex Aldrich Chemicals) and magnesium (4.0 g; 0.17 g atom) in anhydrous ether (250 ml). The reaction mixture was refluxed for 3 hr before it was decomposed with crushed ice and ammonium chloride. The ether layer was separated, dried (Na_2SO_4) and evaporated to dryness to yield the crude basic product. The latter was acidified with ethanolic HCl, cooling the reaction flask in an ice-bath, before the addition of anhydrous ether and storage of the solution at 0° . The initial crystal crop consisted of the ketone precursor (38) hydrochloride (5.3 g), m.p. $151-152^\circ$ which had a characteristic IR spectrum identical to an authentic sample.

Further crops consisted of the butanol (67) hydrochloride (4.8 g; 17%) with m.p. $152-153^\circ$.

IR spectrum (nujol mull): ν_{\max} (C=O) absent,
 ν_{\max} 3270 cm^{-1} (OH).

Found: C, 69.05; H, 9.69. $\text{C}_{18}\text{H}_{29}\text{NO} \cdot \text{HCl}$ requires:
C, 69.33; H, 9.70%.

Acid-Catalysed Elimination of 4-Dimethylamino-1-cyclo-
hexyl-2-phenylbutan-2-ol (67)

The butanol (67) hydrochloride (3.0 g) was dehydrated in the usual manner using an acetic-hydrochloric acid mixture (see p. 256), and fractional crystallisation (EtOH/ether) of the hydrochloride salts yielded the pure cis (H/Ph) but-2-ene (68) hydrochloride, (0.23 g), as colourless crystals, m.p. 243-244° (Frey et al., 1950, gave m.p. 244-245° for an aminobutene hydrochloride of unassigned configuration obtained by dehydration of an unpurified sample of the carbinol (67)).

Found: C, 73.33; H, 9.46. $\text{C}_{18}\text{H}_{27}\text{N} \cdot \text{HCl}$ requires:
C, 73.57; H, 9.60%.

Preparation of 4-Dimethylamino-2-phenyl-1-(2-pyridyl)butan-
2-ol (71)

This tertiary alcohol was prepared by method of Casy and Pocha (1967). Basic β -dimethylaminopropiophenone (38) isolated from its hydrochloride (16.0 g; 0.075 M) was added to lithium 2-picoly, prepared from 2-picoline (23.0 g; 0.25 M), bromobenzene (33.7 g; 0.21 M) and lithium strips

(4.5 g; 0.65 M) in anhydrous ether (250 ml). The reaction mixture was stirred at room temperature overnight and then decomposed with crushed ice. The ethereal phase was dried (CaCl_2), and evaporated down to dryness to afford the crude product (40.8 g; 72%). An IR spectrum of the unpurified carbinol showed the absence of carbonyl peaks and a broad hydroxyl peak was evident (ν_{max} 3500-3100 cm^{-1} , bonded OH). The crude product was then used for the elimination reaction described below.

Acid-Catalysed Dehydration of 4-Dimethylamino-2-phenyl-1(2-pyridyl)butan-2-ol (71)

The carbinol (71) (15 g; 0.06 M) was treated with 85% v.v. aqueous H_2SO_4 (100 ml) and the solution magnetically stirred at 100-110° (oil-bath) for 2.5 hr. The cooled mixture was poured onto crushed ice and basified with strong aqueous ammonia and the products extracted into ether, dried (Na_2SO_4) and the solution concentrated down to a small volume. Acidification with ethanolic HCl would not afford any hydrochloride products and thus the free bases were re-isolated from the mother liquor and treated with a solution of oxalic acid dihydrate (7.0 g) in ethanol (25 ml). Addition of ether and standing at 0° yielded a number of oxalate crops and after numerous recrystallisations from EtOH/ether the following two pure aminobutene isomers were obtained:

cis but-1-ene (74) dihydrogen oxalate, (0.92 g), m.p. 130-131^o.

IR spectrum (nujol mull): ν_{\max} 3300-3150 cm^{-1}
(bonded OH).

Found: C, 58.30; H, 5.65; N, 6.59. $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_8$
requires: C, 58.32; H, 5.59; N, 6.48%.

trans (H/Ph) but-2-ene (73) dihydrogen oxalate, (0.34 g),
m.p. 154-155^o.

IR spectrum (nujol mull); ν_{\max} 3400-3200 cm^{-1}
(bonded OH).

Found: C, 58.80; H, 5.71.

(b) Replacement of the 2-Aryl Ring by the t-Bu Group and
Related Studies

Preparation of 1-t-Butyl-3-dimethylaminopropan-1-one (77)

Pinacolone (49.5 g; 0.49 M), paraformaldehyde (20.0 g; 0.67 M) and dimethylammonium chloride (53.0 g; 0.65 M) were heated under reflux in ethanol (40 ml) containing c-HCl (1 ml) for 6 hr. The cooled mixture was diluted with acetone (250 ml) and stored at 0^o when the Mannich ketone (77) hydrochloride, (82.2 g; 88%) separated, m.p. 173-174^o (EtOH/ether).

IR spectrum (nujol mull): ν_{\max} 1700 cm^{-1} (C=O).

Found: C, 55.79; H, 10.20; N, 7.24. $\text{C}_9\text{H}_{19}\text{NO} \cdot \text{HCl}$
requires: C, 55.80; H, 9.88; N, 7.23%.

Preparation of 2-t-Butyl-4-dimethylamino-1-phenylbutan-2-ol (78)

1-t-Butyl-3-dimethylaminopropan-1-one (77) (27.8 g; 0.18 M) in ether (50 ml) was added to a solution of benzyl-magnesium chloride prepared from benzyl chloride (45 g; 0.36 M) and magnesium (9.7 g; 0.4 g atom) in anhydrous ether (400 ml), the mixture heated under reflux for 2 hr and decomposed with crushed ice and ammonium chloride. The organic phase was dried (MgSO_4), concentrated, and the residue acidified with ethanolic HCl cooling the reaction flask in an ice-bath. Dilution of the solution with ether until close to the coalescence point followed by storage at 0° yielded the carbinol (78) hydrochloride, m.p. 193° (EtOH/ether).

IR spectrum (nujol mull): ν_{max} $3500\text{--}3250\text{ cm}^{-1}$ (bonded OH).

Found: C, 67.38; H, 9.92; N, 4.70. $\text{C}_{16}\text{H}_{27}\text{NO}.\text{HCl}$ requires: C, 67.19; H, 9.51; N, 4.90%.

Acid-Catalysed Elimination of 2-t-Butyl-4-dimethylamino-1-phenylbutan-2-ol (78)

The tertiary alcohol (78) hydrochloride (15 g) was dehydrated in the usual manner using an acetic-hydrochloric acid mixture (see p.256), and fractional crystallisation (EtOH/ether) of the hydrochloride salts over several weeks afforded the following pure aminobutenes in the order given:

trans (t-Bu/H) aminobut-2-ene (79) hydrochloride, (1.08 g),
m.p. 243°.

Found: C, 71.37; H, 9.42; N, 4.89. $C_{16}H_{25}N.HCl$
requires: C, 71.72; H, 9.75; N, 5.23%.

cis (t-Bu/H) aminobut-2-ene (76) hydrochloride, (0.58 g)
m.p. 183-184° (this isomer exhibits a magnetically non-
equivalent t-Bu group in its PMR spectrum - see Table XII).

Found: C, 71.47; H, 9.70; N, 4.99%.

trans (t-Bu/Ph) but-1-ene (81) hydrochloride, (0.36 g),
m.p. 176-177°; λ_{max} 238 m μ (ϵ 8600 in H_2O).

Found: C, 71.54; H, 9.73; N, 5.39%.

Isolation of 1-t-Butyl-1-phenyl-3-dimethylaminopropan-1-ol
(85) and its propene and propane analogues

A mixture of the Mannich base (77) (17.1 g; 0.11 M)
and phenyl-lithium prepared from bromobenzene (17.1 g;
0.11 M), lithium (1.65 g; 0.24 g atom) and anhydrous ether
(100 ml) was heated under reflux for 1 hr before decompo-
sition of the complex with crushed ice and ammonium chloride.
The organic layer was dried ($CaCl_2$) and evaporated to give
a mixture of the unchanged ketone (77) and the expected
butanol (85) (IR spectrum showed both ν_{max} 1705 cm^{-1} (C=O)
and ν_{max} 3430 cm^{-1} OH); fractional crystallisation from
EtOH/ether of the hydrochloride, m.p. 170-175°, obtained
from the mixed base product, failed to separate the

components. A similar product resulted after the Mannich ketone (77) and phenyl-lithium had been heated in toluene at the reflux temperature for 18 hr.

The hydrochloride mixture (6 g) was heated under reflux with acetic acid (40 ml) and concentrated HCl (20 ml) for 4 hr, the base recovered as usual, (its 60 MHz PMR spectrum in CDCl_3 displayed a single vinylic signal at 340 Hz) acidified with ethanolic HCl and fractionally crystallised after dilution of the solution with ether. The products isolated in the same order as given below were:

cis (t-Bu/H) prop-1-ene (86) hydrochloride, (0.45 g), m.p. 250° ; UV absorption spectrum in water showed end-absorption only.

Found: C, 70.76; H, 9.46; N, 5.80. $\text{C}_{15}\text{H}_{23}\text{N}.\text{HCl}$ requires: C, 70.98; H, 9.53; N, 5.52%.

1-t-Butyl-1-phenyl-3-dimethylaminopropan-1-ol (85) hydrochloride, (0.60 g), m.p. $185-187^\circ$.

IR spectrum: (nujol mull) ν_{max} 3390 cm^{-1} (OH) (no carbonyl absorption present).

Found: C, 66.45; H, 9.73; N, 4.95. $\text{C}_{15}\text{H}_{25}\text{NO}.\text{HCl}$ requires: C, 66.28; H, 9.64; N, 5.15%.

A mixture of the aminopropene (86) hydrochloride (0.38 g), 10% palladised charcoal (0.3 g) and ethanol (100 ml) was stirred with hydrogen at atmospheric pressure

and room temperature until gas absorption ceased (5 hr required). The reaction mixture was filtered through kieselguhr and the filtrate evaporated to dryness before the residue was crystallised from acetone to yield 1-t-butyl-3-dimethylamino-1-phenylpropane (87) hydrochloride, 0.30 g), m.p. 201-202°. The 60 MHz spectrum of the product in CDCl₃ (TMS) showed complete absence of any vinylic signals and a sharp t-Bu singlet at 54.5 Hz relative to TMS.

Found: C, 70.22; H, 10.03. C₁₅H₂₅N.HCl requires: C, 70.46; H, 10.24%.

Preparation of 2-t-Butyl-1-o-chlorophenyl-4-dimethylamino-butan-2-ol (88a)

The required butanol (88a) was prepared by treatment of the Mannich base (77) (19.0 g; 0.12 M) with a solution of o-chlorobenzylmagnesium chloride prepared from o-chlorobenzyl chloride (39.0 g; 0.24 M) (Ex Aldrich Chemicals) and magnesium (7.3 g; 0.3 g atom) in anhydrous ether (300 ml). The reaction work-up was identical to that employed for the phenyl analogue (78) previously described and the butanol (88a) hydrochloride, (23.5 g; 61%) separated as colourless prisms, m.p. 174° (EtOH.ether).

IR spectrum (nujol mull): ν_{\max} 3360 cm⁻¹ (OH).

Found: C, 60.21; H, 8.65; N, 4.21. C₁₆H₂₆ClNO.HCl requires: C, 59.98; H, 8.50; N, 4.37%.

Acid-Catalysed Elimination of 2-t-Butyl-1-o-chlorophenyl-4-dimethylaminobutan-2-ol (88a)

The butanol (88a) hydrochloride (13 g) was dehydrated

in the same manner as the phenyl analogue (78) and subsequent fractional crystallisation (EtOH/ether) of the hydrohalide mixtures over a period of several weeks yielded the following aminobutenes in the order given:

trans (t-Bu/H) but-2-ene (90) hydrochloride, (0.78 g) m.p. 233-234°.

Found: C, 63.83; H, 8.54; N, 4.36. $C_{16}H_{24}ClN.HCl$ requires: C, 63.57; H, 8.34; N, 4.63%.

cis (t-Bu/H) but-2-ene (89) hydrochloride, (0.60 g), m.p. 195-196° (this isomer exhibits a magnetically non-equivalent t-Bu group in its PMR spectrum - see Table XII).

Found: C, 63.76; H, 8.60; N, 4.41%.

trans (t-Bu/Ar) but-1-ene (91) hydrobromide (1.83 g), m.p. 175°; UV absorption spectrum in water showed end absorption only.

Found: C, 55.27; H, 7.40; N, 4.17. $C_{16}H_{24}ClN.HBr$ requires: C, 55.42; H, 7.27; N, 4.04%.

Reaction of the t-Bu Mannich base (77) with 2,6-dichlorobenzylmagnesium bromide and dehydration of the product

The aminoketone (77) (15.0 g; 0.096 M) was added dropwise to a Grignard reagent prepared from 2,6-dichlorobenzyl bromide (45.8 g; 0.19 M) (Ex Aldrich Chemicals), magnesium (4.9 g; 0.2 g atom) and anhydrous ether (250 ml), and the mixture heated under reflux for 2.5 hr, before decomposition with crushed ice and ammonium chloride. The

ethereal layer was dried (Na_2SO_4), concentrated down to small volume and the basic product acidified with ethanolic HCl , cooling the reaction flask in an ice-bath to prevent dehydration. Dilution with ether and cooling to 0° yielded a hydrochloride (14.1 g), m.p. $150\text{--}160^\circ$, composed of the unchanged ketone starter (77) and the butanol product (88b) (IR evidence), and a pure crop of 1-t-butyl-1-phenyl-3-dimethylaminopropan-1-ol (85) hydrochloride, (0.8 g), m.p. and mixed m.p. $185\text{--}187^\circ$ (IR and PMR spectra identical with those of authentic sample).

Found: C, 66.55; H, 9.64; $\text{C}_{15}\text{H}_{25}\text{NO} \cdot \text{HCl}$ requires C, 66.28; H, 9.64%.

The mixed hydrochloride crop, composed of (77 and 88b), could not be resolved by fractional crystallisation (EtOH/ether) and thus the total base (10 g) mixture was recovered and treated with a mixture of acetic and hydrochloric acids as before. Subsequent fractional crystallisation from EtOH/ether of the acidified reaction product lead to the isolation of the following products:

cis (t-Bu/H) prop-1-ene (86) hydrochloride, (0.58 g), m.p. and mixed m.p. $242\text{--}243^\circ$ and IR and PMR spectra all identical to those of authentic sample.

cis (t-Bu/H) but-2-ene (92) hydrochloride, (0.39 g), m.p. $208\text{--}210^\circ$ (this isomer exhibited a magnetically non-equivalent t-Bu group in its PMR spectrum - see Table XII).

Found: C, 57.36; H, 7.39; N, 4.07. $C_{16}H_{23}Cl_2N.HCl$ requires: C, 57.07; H, 7.19; N, 4.16%.

trans (t-Bu/H) but-2-ene (93) hydrobromide, (0.25 g),
m.p. 223° .

Found: C, 50.70; H, 6.54; N, 3.49. $C_{16}H_{23}Cl_2N.HBr$ requires: C, 50.42; H, 6.35; N, 3.68%.

Experimental Checks for Possible Contamination with Bromobenzene of the Commercial Sample of 2,6-dichlorobenzyl Bromide Used in the Above Reactions

The m.p., micro-analysis and PMR studies (see main text, p. 101 et seq.) all suggested that the 2,6-dichlorobenzyl bromide (Ex Aldrich Chemicals) was of high purity.

A final check by GLC was carried out using an F and M Scientific 700 Laboratory Chromatograph incorporating a hydrogen flame ionisation detector.

A 6 ft 1% silicon gum rubber column, diameter 1/8", with OV-17, 80-100 mesh DMCS stationary phase at 120° was employed for the experiments; the temperatures at the injection port and the detector were 260° and 280° respectively. Initially, the purity of the ether solvent used for this study was checked and then a 2 μ l aliquot of a solution of 2,6-dichlorobenzyl bromide (13.5 mg/ml) in ether was run under the conditions given above. A single peak was observed for this compound with a retention time of 20.5 min.

A 2 μ l aliquot of a solution of bromobenzene (12.0 mg/ml) in ether was then injected into the chromatograph and a single peak (retention time 1.2 min) was again observed. Careful re-examination of the recorder chart for the dichloro compound showed absolutely no trace of any peak at the 1.2 minute mark. Addition of bromobenzene to the pure dichloro solution did, however, provide the expected two peaks at 20.5 and 1.2 min retention times. These observations gave final and conclusive proof of the high purity of the sample of 2,6-dichlorobenzyl bromide used in the previously discussed Grignard reactions.

Reaction of 2,6-Dichlorobenzyl magnesium bromide with the less crowded Mannich base (38)

3-Dimethylamino-1-phenylpropan-1-one (38) free base, isolated from the hydrochloride salt (16.0 g; 0.075 M) was treated with a Grignard reagent prepared from 2,6-dichlorobenzyl bromide (35.9 g; 0.15 M) and magnesium (4.9 g; 0.2 g atom) as before. The base product after acidification with ethanolic hydrogen chloride yielded crops of the ketone substrate hydrochloride (0.58 g) (IR spectrum, m.p. and mixed m.p. identical to those of authentic material) and 1-(2,6-dichlorophenyl)-4-dimethylamino-2-phenylbutan-2-ol (94) hydrochloride, (11.2 g; 40%), m.p. 234-235^o (EtOH/ether).

IR spectrum (nujol mull); ν_{\max} 3240 cm^{-1} (OH). PMR characteristics at 60 MHz in DMSO- d_6 (10% w/v) relative to

TMS: 8 proton aryl signal at 441 Hz; CH_2Ar , broad singlet, 204 Hz; NMe_2 , singlet, 160 Hz; the hydroxyl signal was at 318 Hz (broad singlet, which collapsed after the addition of a drop of D_2O).

Found: C, 57.64; H, 5.65. $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{NO} \cdot \text{HCl}$ requires: C, 57.71; H, 5.92%.

EXPERIMENTAL WORK RELEVANT TO CHAPTER 4, AMINOPROPENES
AND RELATED COMPOUNDS

Synthesis of 3-Dimethylamino-1-phenyl-1-(2-pyridyl)propan-
1-ol (98)

(a) Initially an ethereal solution of n-butyl-lithium was prepared by the method of Akhtar and Barton (1964) as follows: A magnetically stirred suspension of lithium strips (2.8 g; 0.404 M) in anhydrous ether (100 ml) was cooled to -10° (acetone/ CO_2 bath) and a slow stream of nitrogen gas was bubbled through the mixture. n-Butyl bromide (27.4 g; 0.2 M) was then added dropwise to the suspension keeping the temperature between -10 and 0° , after which the reaction mixture was stirred under nitrogen between -10 and $+10^{\circ}$ for 2.5 hr.

(b) The aforementioned metalating reagent was then used to generate a solution of 2-pyridyl-lithium using the technique of Adamson and Billingham (1950).

The n-butyl-lithium solution was cooled to -60° (acetone/ CO_2 bath) and 2-bromopyridine (31.6 g; 0.2 M) was added dropwise over 15 min, keeping the temperature of the mixture between -60 and -50° and continuing to bubble nitrogen gas into the reaction flask. The brown complex was then stirred at -60 to 50° under nitrogen for 1.5 hr after which a solution of the Mannich ketone (38) (31.4 g; 0.18 M) in ether (50 ml) was added at -50° .

The reaction mixture was stirred for a further 1.5 hr at -60 to -50° before being allowed to warm to room temperature. The suspension was then decomposed with crushed ice and the dark-red ether layer separated and dried (Na_2SO_4). Evaporation of the solution under reduced pressure yielded the crude product as a dark-red oil. The latter was treated with hexane (200 ml) and the mixture refluxed for 0.5 hr before filtering the solution free of insoluble, tarry, bi-products. The filtrate was concentrated down to dryness and the residual oil solidified on cooling. The product was immediately recrystallised from EtOH/charcoal to afford buff crystals of 3-dimethylamino-1-phenyl-1-(2-pyridyl)propan-1-ol (98), (23.1 g; 53%), m.p. $92-93^{\circ}$. A second recrystallisation elevated the m.p. to $97-99^{\circ}$ (Adamson and Billingham, 1950, gave m.p. $99-100^{\circ}$).

IR spectrum (5% CCl_4): ν_{max} 3450-3100 (strongly bonded OH).

Acid-Catalysed Dehydration of 3-Dimethylamino-1-phenyl-1-(2-pyridyl)propan-1-ol (98)

Dehydration of the carbinol (98) was achieved after following the method of Adamson *et al.* (1958). The substrate (6.9 g) was dissolved in 85% v.v. aqueous H_2SO_4 (100 ml) and the solution stirred at $100-110^{\circ}$ (oil-bath) for 2 hr to allow for equilibration of the isomeric

products. After cooling, the reaction mixture was poured onto crushed ice and basified with strong aqueous ammonia before the product was extracted into ether and dried (Na_2SO_4). Evaporation of the ethereal solution afforded the total base product (examined by PMR at this point) which was dissolved in ethanol (50 ml) and treated with an ethanolic solution of oxalic acid dihydrate (2.7 g). Dilution with ether and fractional crystallisation yielded:

trans (2-pyridyl/ CH_2N) prop-1-ene (99) oxalate, (1.14 g), m.p. 176° (Adamson et al., 1957, gave m.p. 179°).

UV characteristics (EtOH): λ_{max} 245 m μ (ϵ 7800) and λ_{max} 283 m μ (ϵ 5700) (2-vinylpyridine type) [Adamson et al., 1957, gave λ_{max} 238 m μ ($\log \epsilon$ 4.32) and λ_{max} 280 m μ ($\log \epsilon$ 4.03) (EtOH/ CHCl_3)].

Found: C, 65.56; H, 6.26; N, 8.37. $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$ requires: C, 65.82; H, 6.14; N, 8.53%.

cis (2-pyridyl/ CH_2N) prop-1-ene (100) oxalate, (0.76 g), m.p. $178-179^\circ$ (Adamson et al., 1957, gave m.p. $180-181^\circ$).

UV characteristics (EtOH): λ_{max} 252 m μ (ϵ 10,000) (styrenoid type) [Adamson et al., 1957, gave λ_{max} 247 ($\log \epsilon$ 4.35) (EtOH/ CHCl_3)].

Found: C, 65.81; H, 6.03; N, 8.73. $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$ requires: C, 65.82; H, 6.14; N, 8.53%.

Synthesis of the 'Triprolidine' Isomers

Preparation of 3-(1-Pyrrolidino)-1-p-tolylpropan-1-one
(103)

An aqueous solution of pyrrolidine hydrochloride was prepared by careful acidification of pyrrolidine free base (35.6 g; 0.5 M) with concentrated HCl, cooling in an ice-bath. Paraformaldehyde (22.0 g; 0.7 M), p-methyl-acetophenone (60 g; 0.448 M) and ethanol (100 ml) were then added to the reaction flask and the mixture heated under reflux for 13 hr. Dilution of the cooled solution with ether and storage at 0° failed to separate the product which suggested that the Mannich hydrochloride was extremely water soluble. Accordingly, a Dean-Stark head was attached to the reaction flask and after addition of some benzene (200 ml) the water (and ethanol) present were removed by azeotropic distillation. The residual solution was evaporated to dryness and the solid mass triturated with ethyl acetate which led to separation of the crystalline product. Recrystallisation from EtOH/ether gave the pure 3-(1-pyrrolidino)-1-p-tolylpropan-1-one (103) hydrochloride, (56.2 g; 50%), m.p. 167° (Adamson et al., 1958, gave m.p. 170°).

IR spectrum (nujol mull); ν_{\max} 1680 cm^{-1} (C=O).

PMR characteristics of the free base in CDCl_3 (TMS) at 60 MHz: Aromatic A_2B_2 quartet, 453 Hz (centre); $\text{CH}_2\text{CH}_2\text{N}$,

182 Hz (centre of A_2B_2 multiplet); Aryl Me, 144 Hz (singlet).

Preparation of 1-(2-Pyridyl)-3-(1-pyrrolidino)-1-p-tolylpropan-1-ol (104)

This tertiary alcohol was synthesized in the same manner as the 3-dimethylamino-1-phenyl analogue (98) using n-butyl bromide (20.6 g; 0.15 M), lithium (2.1 g; 0.3 g atom), 2-bromopyridine (17.3 g; 0.11 M) and the appropriate Mannich base (103) isolated from its hydrochloride salt (25.4 g; 0.1 M). The product separated as buff crystals of 1-(2-pyridyl)-3-(1-pyrrolidino)-1-p-tolylpropan-1-ol (104), (8.3 g; 28%), m.p. 116-117^o (EtOH) (Adamson et al., 1958, gave m.p. 119-120^o).

IR spectrum (10% CCl_4): ν_{max} 3450-3100 (strongly bonded OH).

Acid-Catalysed Dehydration of 1-(2-pyridyl)-3(1-pyrrolidino)-1-p-tolylpropan-1-ol (104)

Dehydration of the carbinol (104) (7.0 g) using 85% H_2SO_4 over a 2 hr period yielded solely the thermodynamically controlled trans (2-pyridyl/ CH_2N) product (14) (PMR evidence). Acidification with a solution of oxalic acid dihydrate (3.0 g) in ethanol (50 ml) yielded buff crystals of the trans (2-pyridyl/ CH_2N) prop-1-ene (14) oxalate, (5.6 g) ('Triprolidine' oxalate), m.p. 171^o (Adamson et al., 1958, gave m.p. 173-174^o).

UV characteristics (EtOH): λ_{\max} 238 m μ (ϵ 14700) and 283 m μ (ϵ 6650) (2-vinylpyridine type) [Adamson et al., 1958, gave λ_{\max} 233 m μ (ϵ 16200) and 283 m μ (ϵ 8200) (EtOH)].

Kinetic control of the elimination reaction was achieved, however, by dehydration of the alcohol (4.5 g) over only a 15 min heating period (Adamson and Billingham, 1950, have discussed this effect); fractional crystallisation of the oxalates from EtOH/ether yielded the pure cis (2-pyridyl/CH₂N) prop-1-ene (105) oxalate, (2.46 g), m.p. 147-148° (Adamson et al., 1958, gave m.p. 149-150°).

UV characteristics (EtOH): λ_{\max} 244 m μ (ϵ 14100) and 258 m μ (ϵ 14500) (styrenoid type) [Adamson et al., 1958, gave λ_{\max} 233 m μ (ϵ 13600) and 260 m μ (ϵ 13800) (EtOH)].

Synthesis of Aminopropenes Containing Methyl Groups

Preparation of 3-Dimethylamino-1-(2-pyridyl)-1- α -tolylpropan-1-ol (106)

Synthesis of the required carbinol (106) was carried out in the usual way using n-butyl bromide (30.1 g; 0.22 M), lithium (3.2 g; 0.47 M), 2-bromopyridine (34.4 g; 0.22 M) and the appropriate aminoketone (62) (36.6 g; 0.19 M). A low yield of 3-dimethylamino-1-(2-pyridyl)-1- α -tolylpropan-1-ol (106), (5.1 g; 11%), m.p. 96°, was thus obtained.

IR spectrum (10% CCl₄): ν_{\max} 3480-3150 cm⁻¹ (strongly bonded OH).

Found: C, 75.82; H, 8.40. $C_{17}H_{22}N_2O$ requires:
C, 75.51; H, 8.20%.

Acid-Catalysed Elimination of 3-Dimethylamino-1-(2-pyridyl)-
1- α -tolylpropan-1-ol (106)

Dehydration of the tertiary alcohol (106) (5.0 g) over a 2.5 hr period using 85% H_2SO_4 at $100-110^\circ$, followed by the usual reaction work-up yielded the basic isomeric products. Fractional crystallisation of the oxalate salts from EtOH/ether yielded a pure sample of the trans (2-pyridyl/ CH_2N) prop-1-ene (107) oxalate, (1.65 g), m.p. 160° (dec.).

UV characteristics (EtOH): λ_{max} 233 m μ (ϵ 14600) and λ_{max} 282 m μ (ϵ 7500) (2-vinylpyridine type).

Found: C, 66.62; H, 6.50; N, 8.11. $C_{19}H_{22}N_2O_4$ requires: C, 66.65; H, 6.48; N, 8.19%.

Also isolated were a number of mixed oxalate crops of both geometrical isomers from which relevant PMR data for the cis oxalate (108) were obtained (see Table XVI). Liberation of the bases from the mother liquors and re-acidification with ethanolic hydrogen bromide led to the isolation of 50:50 mixture (PMR Integral data) of cis and trans aminopropene dihydrobromides (107 and 108), (0.61 g), m.p. $213-214^\circ$ (dec.) (EtOH/ether).

Found: C, 49.08; H, 5.54. $C_{17}H_{20}N_2 \cdot 2HBr$ requires: C, 49.29; H, 5.36%.

Preparation of the Mannich Ketone Precursors Required
for Synthesis for the 2-Methylaminopropenes

The following compounds were prepared by the Mannich reaction as previously described (see p. 253 et seq.):

3-Dimethylamino-2-methyl-1-phenylpropan-1-one (109) hydrochloride, yield 63%, m.p. 153° (EtOH/ether) (Buckley and Ruddy, 1950, gave m.p. $153-154^{\circ}$).

2-Methyl-1-phenyl-3-(1-pyrrolidino)propan-1-one (110) hydrochloride, yield 50%, m.p. 150° (EtOH/ether) (Adamson et al., 1958, gave m.p. $149-150^{\circ}$).

2-Methyl-1-phenyl-3-(1-piperidino)propan-1-one (111) hydrochloride, yield 60% (only after a 66 hr reflux period - no product could be isolated after a 4 hr heating period), m.p. $176-177^{\circ}$ (EtOH/ether) (Buckley and Ruddy, 1950, gave m.p. $176-177^{\circ}$).

All the ketones described above exhibited strong IR ν_{\max} (C=O) absorption bands in the $1700-1680\text{ cm}^{-1}$ region.

Preparation of the 3-Amino-2-methyl-1-phenyl-1-(2-pyridyl)-propan-1-ols (112)

The following intermediates were synthesized in the usual manner by reaction of 2-pyridyl-lithium with the appropriate Mannich ketones:

3-Dimethylamino-2-methyl-1-phenyl-1-(2-pyridyl)propan-1-ol (112a), yield 49% (using 0.15 M of the aminoketone substrate), m.p. 74-75° (EtOH).

Found: C, 75.63; H, 8.01; N, 10.10. $C_{17}H_{22}N_2O$ requires: C, 75.51; H, 8.20; N, 10.36%.

2-Methyl-1-phenyl-3-(1-pyrrolidino)propan-1-ol (112b), yield 9% only (using 0.06 M of the aminoketone substrate), m.p. 112° (hexane) (Adamson et al., 1958, gave m.p. 111°).

2-Methyl-1-phenyl-3-(1-piperidino)propan-1-ol (112c), yield 18% (using 0.06 M of the aminoketone substrate), m.p. 125-126° (hexane) (Adamson et al., 1958, gave m.p. 134°).

Found: C, 77.44; H, 8.36; N, 9.26. $C_{20}H_{26}N_2O$ requires: C, 77.38; H, 8.44; N, 9.03%.

All the above carbinols exhibited IR ν_{\max} (bonded OH) absorption bands in the 3400-3100 cm^{-1} region (10% CCl_4 solutions).

Acid-Catalysed Dehydration of the 3-Amino-2-methyl-1-phenyl-1-(2-pyridyl)propanols (112)

- (a) Formation of the 3-Dimethylamino-2-methylaminopropanes (113 and 114)

Dehydration of the carbinol (112a) (8.7 g) using 85% H_2SO_4 at 100-110° over a 1.5 hr period, followed by the usual reaction work-up afforded the basic isomeric

products. Fractional crystallisation of the oxalate salts from EtOH/ether yield a pure sample of cis (2-pyridyl/CH₂N)2-methylprop-1-ene (114) oxalate, (2.01 g), m.p. 184-185°.

Found: C, 66.76; H, 6.58; N, 8.08. C₁₉H₂₂N₂O₄ requires: C, 66.65; H, 6.48; N, 8.19%.

Also isolated was a mixed oxalate crop composed of 70% of the trans and 30% of the cis (2-pyridyl/CH₂N)-2-methylprop-1-ene oxalates (113 and 114) (PMR integral evidence), (2.04 g), m.p. 158°.

(b) Formation of the 3-(1-Pyrrolidino)-2-methylaminopropenes (115 and 116)

Dehydration of the tertiary alcohol (112b) (1.43 g) by the usual method afforded the isomeric aminopropene mixture. Acidification of the latter with ethanolic oxalic acid and a fractional crystallisation would only afford an enriched mixture composed of 85% of the cis and 15% of the trans (2-pyridyl/CH₂N)-2-methylprop-1-ene oxalates (116 and 115 respectively) (PMR integral evidence), (0.35 g), m.p. 154-155° (EtOH/ether).

Found: C, 68.22; H, 6.36. C₂₁H₂₄N₂O₄ requires: C, 68.45; H, 6.57%.

(c) Formation of the 3-(1-Piperidino)-2-methylaminopropenes (117 and 118)

Acid-catalysed elimination of the carbinol (112c)

(3.0 g) over a 2 hr period afforded, at what first appeared, a single aminopropene (PMR evidence, see p. 140 for discussion). A repeat elimination using only a 15 min heating period yielded a product with an identical PMR spectrum to that obtained from the original experiment.

Acidification of the basic product derived from the 2 hr dehydration reaction with ethanolic oxalic acid yielded a 50:50 mixture of the cis and trans aminopropene oxalates (117 and 118) (1.84 g) but numerous recrystallisations (EtOH/ether) of the product failed to alter the m.p. (159-160°) or the overall composition (PMR evidence) of the mixed crystals.

Found: C, 69.25; H, 6.82. $C_{22}H_{26}N_2O_4$ requires: C, 69.07; H, 6.85%.

Synthesis of 3-Amino-1,1-diarylprop-1-enes

Preparation of the 3-Amino-1-diphenylpropan-1-ol (119)

Intermediates

(a) 3-Dimethylamino derivative

This compound was prepared by the method of Adamson (1949) as follows: the Mannich ketone (38) (14.2 g; 0.08 M) was treated with a solution of phenyl-lithium prepared from bromobenzene (15.7 g; 0.1 M) and lithium strips (1.39 g; 0.2 g atom) in anhydrous ether (250 ml), and the mixture

refluxed for 3 hr. The complex was decomposed by pouring onto crushed ice and ammonium chloride and the ethereal phase was filtered free of the suspended product. The residue obtained from the organic layer was added to the first product before recrystallisation of the total crude mixture from benzene. The product separated out as colourless crystals of 3-dimethylamino-1-diphenylpropan-1-ol (119a), (10.3 g; 51%), m.p. 164-165^o (Adamson, 1949, gave m.p. 166^o).

(b) 3-(1-Pyrrolidino) derivative

This compound was similarly prepared by Adamson's method (1949) using 0.05 mole of the Mannich ketone (42). The product formed cream coloured crystals of 1-diphenyl-3-(1-pyrrolidino)propan-1-ol (119c) (5.9 g; 42%), m.p. 168-169^o (EtOAc) (Adamson, 1949, gave m.p. 171^o).

Acid-Catalysed Elimination of the Amino-propan-1-ols (119a, 119c, 120 and 122)

The 3-amino-1-diphenylpropan-1-ol (119) precursors were both dehydrated by the method of Casy and Pocha (1967) using an acetic-hydrochloric acid mixture (see p. 256 for general method). Acidification of the basic products in each case with ethanolic HCl afforded:

3-dimethylamino-1-diphenylprop-1-ene (95a) hydrochloride, m.p. 168^o (EtOH/ether) (Adamson, 1949, gave m.p. 168-170^o).

1-diphenyl-3-(1-pyrrolidino)prop-1-ene (95c) hydrochloride, m.p. 163° (EtOH/ether) (Adamson, 1949, gave m.p. $165-167^{\circ}$).

Samples of 3-dimethylamino-1-diphenyl-2-methylpropan-1-ol (120) and its 2-Me analogue (122), prepared by the method of Kjaer and Peterson (1951), were kindly supplied by Dr. M.M.A. Hassan of the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta. Dehydration of these compounds using acetic-hydrochloric acid mixtures yielded:

3-dimethylamino-1-diphenyl-2-methylprop-1-ene (121) hydrochloride, m.p. 190° (EtOH/ether) (Kazaryan and Nazarov, 1957, gave m.p. 191°).

3-dimethylamino-1-diphenyl-3-methylprop-1-ene (123) hydrochloride, m.p. 161° (EtOH/ether) (Armstrong et al., 1961, gave m.p. $162-163^{\circ}$).

Preparation of 1-Phenyl-3-(1-pyrrolidino)-1-p-tolylpropan-1-ol (124)

Treatment of the Mannich ketone (103) with phenyllithium in ether at reflux temperature over a 2 hr period failed to produce any of the required carbinol product (the IR spectrum of the recovered base was identical to the authentic aminoketone precursor).

However, when the aminoketone (103) base (isolated from 20.3 g, 0.08 M, of the hydrochloride) was treated

with phenyl-lithium prepared from bromobenzene (15.7 g; 0.10 M) and lithium (1.39 g; 0.20 g atom) in ether (350 ml), and the latter solvent was removed by distillation after the addition of anhydrous toluene (350 ml), heating in the higher boiling point (120°) solvent produced the tertiary alcohol (124) in low yield. Decomposition of the lithium complex with crushed ice and ammonium chloride and evaporation of the dried (MgSO_4) organic layer, before acidification of the residue with ethanolic HCl , yielded 1-phenyl-3-(1-pyrrolidino)-1-p-tolylpropan-1-ol (124) hydrochloride, (4.03 g; 16%), m.p. $167-168^{\circ}$ (EtOH/ether).

IR spectrum (nujol mull): ν_{max} 3250 cm^{-1} (OH).

Found: C, 72.21; H, 8.05. $\text{C}_{20}\text{H}_{25}\text{NO} \cdot \text{HCl}$ requires: C, 72.38; H, 7.90%.

Preparation of 3-(1-Pyrrolidino)-1-di-p-tolylpropan-1-ol
(126)

The Mannich base (103) (isolated from 25.4 g, 0.10 M, of the hydrochloride) was treated with a solution of p-tolyl-lithium which was prepared with some difficulty (even after rigorous drying of all the apparatus and reagents) from 4-bromotoluene (20.0 g; 0.117 M) and lithium strips (1.63 g; 0.234 g atom) in anhydrous ether (400 ml). The mixture was heated at reflux temperature for 1.5 hr before pouring onto crushed ice and ammonium chloride and separating and drying (Na_2SO_4) the ethereal phase. Evaporation

of the latter yielded the basic product as an oily solid which separated out as colourless crystals of 3-(1-pyrrolidino)-1-di-p-tolylpropan-1-ol (126), (18.4 g; 60%), m.p. 131-132°, after the addition of some ethanol.

IR spectrum (nujol mull): ν_{\max} 3180 cm^{-1} (OH).

Found: C, 81.64; H, 8.59. $\text{C}_{21}\text{H}_{27}\text{NO}$ requires:
C, 81.49; H, 8.80%.

Acid-Catalysed Dehydration of the 3-(1-Pyrrolidino)-p-tolylpropan-1-ols (124 and 126)

Both carbinols were eliminated using an acetic-hydrochloric acid mixture (see p. 256, for general method).

Thus, 1-phenyl-3-(1-pyrrolidino)-1-p-tolylpropan-1-ol (124) hydrochloride, (3.9), gave a 50:50 mixture (PMR integral evidence) of the cis and trans 1-phenyl-3-(1-pyrrolidino)-1-p-tolylprop-1-ene hydrochlorides (125), (1.83 g), m.p. 143-144° (EtOH/ether).

Found: C, 76.54; H, 7.83. $\text{C}_{20}\text{H}_{23}\text{N.HCl}$ requires:
C, 76.30; H, 7.68%.

Similarly, 3-(1-pyrrolidino)-1-di-p-tolylpropan-1-ol (126), (3.0 g), yielded 3-(1-pyrrolidino)-1-di-p-tolylprop-1-ene (127) hydrochloride, (1.97 g), m.p. 217° (EtOH/ether).

Found: C, 76.82; H, 7.99. $\text{C}_{21}\text{H}_{25}\text{N.HCl}$ requires:
C, 76.91; H, 8.00%.

Attempts to Introduce the 2-Pyridyl Heterocycle into an Aminobutenic Structure

Attempted Preparation of 3-Dimethylamino-1-(2-pyridyl)-propan-1-one (129)

2-Acetylpyridine (12.1 g; 0.10 M) (Ex Aldrich Chemicals), dimethylamine hydrochloride (10.2 g; 0.125 M) and paraformaldehyde (4.1 g; 0.135 M) were dissolved in a mixture of ethanol (50 ml) and concentrated HCl (20 ml), and the solution heated under reflux for 6 hr. A tarry black solution resulted and after removal of the water present, by addition of benzene (200 ml) and azeotropic distillation using a Dean-Stark head, an intractable black tar was obtained.

The same sequence of events occurred when the above reaction was repeated (on the same scale) under an atmosphere of nitrogen.

Preparation of 3-Dimethylamino-1-(3-pyridyl)propan-1-one (131)

This compound was synthesized by modification of the literature method of McElvain and Snell (1934) as follows: 3-Acetylpyridine (24.2 g; 0.20 M) (Ex Koch-Light Chemicals), dimethylamine hydrochloride (20.4 g; 0.25 M) and paraformaldehyde (8.2 g; 0.27 M) were dissolved in a solution of ethanol (150 ml) and concentrated

HCl (40 ml), and the mixture refluxed for 23 hr. The water present was removed by azeotropic distillation (benzene, Dean-Stark head) and the solution concentrated down to dryness under reduced pressure. The residual syrup was treated with ethanol (100 ml) and after storage of the solution at 0°, cream crystals of the Mannich ketone (131) dihydrochloride, (17.7 g; 35%), separated, m.p. 179-180° (McElvain and Snell, 1934, gave m.p. 178-180°).

IR spectrum (nujol mull): ν_{\max} 1700 cm^{-1} (C=O).

A previous experiment under the same conditions as those above, but using only 2 ml of concentrated HCl (according to the literature method) afforded no reaction and only the isolation of unchanged ketone substrate (IR evidence).

Attempted preparation of 4-Dimethylamino-1-phenyl-2-(3-pyridyl)butan-2-ol

Treatment of the Mannich base (131), isolated from its dihydrochloride (16.0 g; 0.064 M), with benzylmagnesium chloride prepared from benzyl chloride (15.2 g; 0.12 M) and magnesium (2.9 g; 0.12 g atom) in anhydrous ether (300 ml) yielded only unchanged ketone precursor (IR evidence) after the reaction mixture had been worked up in the usual way following a 3.0 hr reflux period.

A repeat reaction attempt conducted in toluene (400 ml) also afforded only the unchanged ketone after heating for 24 hr at the higher reflux temperature.

Reaction of Phenylacetone under Mannich Conditions

Phenylacetone (67.1 g; 0.50 M), dimethylamine hydrochloride (52.7 g; 0.65 M) and paraformaldehyde (19.8 g; 0.66 M) were heated at reflux temperature in ethanol (80 ml) containing concentrated HCl (2 ml) over a period of 5 hr. The reaction mixture was cooled and ether added until the solution was close to the coalescence point. Storage at 0° afforded the crude aminoketone (133) hydrochloride, (82.6 g; 73%). Recrystallisation from isopropanol gave the pure 4-dimethylamino-3-phenylbutan-2-one hydrochloride (133), product as colourless prisms, m.p. 152° (Kyi and Wilson, 1952, gave m.p. 155-156°).

IR spectrum (nujol mull): ν_{\max} 1720 cm^{-1} (C=O)

Reaction of 4-Dimethylamino-3-phenylbutan-2-one with Phenyl-lithium

The aminoketone base (23.3 g; 0.122 M) was treated with phenyl-lithium prepared from bromobenzene (21.1 g; 0.134 M) and lithium (1.91 g; 0.275 M) in ether (150 ml) at reflux temperature for 3 hr. The mixture was then poured onto crushed ice and ammonium chloride and the organic layer separated and dried (CaCl_2). Evaporation

of the ethereal solution yielded the crude 4-dimethylamino-2,3-diphenylbutan-2-ol (134) product, (23.8 g; 73%) which was immediately used for the elimination reaction described below:

IR spectrum (thin film): ν_{\max} C=O (absent, ν_{\max} 3400 cm^{-1} (bonded OH).

Acid-Catalysed Elimination of 4-Dimethylamino-2,3-diphenylbutan-2-ol (134)

The carbinol (134) (22.8 g) was dehydrated with an acetic-hydrochloric acid mixture in the usual manner.

Fractional crystallisation of the acidified products gave:

trans-4-dimethylamino-2,3-diphenylbut-2-ene (135) hydrochloride, (4.85 g), m.p. 234-235° (EtOH/Ether).

UV spectrum: λ_{\max} 249 m μ (ϵ 9840) (H_2O). PMR characteristics at 60 MHz in CDCl_3 (TMS): 10 proton aryl broad singlet, 426 Hz; CH_2N , doublet, 261 Hz (J_{NH}^+ 4.5); NMe_2 , doublet, 161 Hz (J_{NH}^+ 4.5); $=\text{C-Me}$, singlet, 146 Hz.

Found: C, 74.99; H, 7.83; N, 4.88. $\text{C}_{18}\text{H}_{21}\text{N}.\text{HCl}$ requires: C, 75.11; H, 7.71; N, 4.8%.

4-dimethylamino-2,3-diphenylbut-1-ene (136) hydrochloride, (4.48 g), m.p. 188° (EtOH/ether).

UV spectrum: λ_{\max} 235 m μ (ϵ 8570) (H_2O). PMR characteristics at 60 MHz in CDCl_3 (TMS): $=\text{C-H}$'s, singlets, 333

and 318 Hz; >C-H , triplet, 289 Hz (J_7); CH_2N , broad band centred at 215 Hz; NMe_2 , doublet of doublets centred at 160 Hz (J_{NH}^+ 4.5).

Found: C, 74.99; H, 7.62; N, 4.79.

Condensation of Dimethylamine with Ethyl Acrylate

Anhydrous dimethylamine (100 g; 2.22 M) (contained in ampoules which were cooled in an acetone/ CO_2 bath before opening because of the low b.p. (7°) of the secondary amine) was dissolved in absolute methanol (500 ml) and the solution cooled to -30° (acetone/ CO_2 bath). Ethyl acrylate (180 g; 1.80 M) was added dropwise over 20 min, keeping the temperature at -40 to -30° before the mixture was stirred at -30 to -10° for 5 hr. The reaction mixture was then allowed to warm to room temperature before stirring the cherry-red solution overnight after which the methanol was carefully removed under reduced pressure.

Distillation of the residue at atmospheric pressure yielded 2-dimethylamino-ethylpropionate (137), (171.5 g; 66%), b.p. 147° (Tammelin, 1957, gave b.p. $59^\circ/10$ mm).

IR spectrum (thin film): ν_{max} 1745 cm^{-1} (C=O). PMR characteristics at 60 MHz in CDCl_3 (TMS): CH_2Me , quartet, 247 Hz ($J_{7.5}$); CH_2CH_2 , centre of A_2B_2 multiplet, 160 Hz; NMe_2 , singlet, 134 Hz; CH_2Me , triplet, 75 Hz (J 7.5).

A sample of the base formed the hydrobromide, m.p. 113° (EtOH/ether) (Tammelin, 1957, gave m.p. 112°). PMR characteristics at 60 MHz in D_2O (DSS): $\underline{CH_2}Me$, quartet, 253 Hz (J7); $\underline{CH_2CH_2}$, deformed triplets (J6) at 209 and ca. 175 Hz (masked by NMe_2^+ band); NMe_2 , singlet, 175.5 Hz; $\underline{CH_2Me}$, 75.5 Hz).

Preparation of 4-Dimethylamino-2-benzylbutan-2-ol (138)

The ester (137) (29.0 g; 0.20 M), was treated with benzylmagnesium chloride prepared from benzyl chloride (63.3 g; 0.5 M) and magnesium (13.6 g; 0.6 g atom) and the mixture heated at reflux temperature for 5.5 hr. The complex was then decomposed with crushed ice and ammonium chloride and the organic layer separated and dried (Na_2SO_4). Evaporation of the ethereal solution gave the basic product which was acidified with ethanolic HCl (cooling the reaction mixture in an ice-bath). The product immediately separated out as colourless crystals of the carbinol hydrochloride, (39.1 g; 61%), m.p. $177-178^{\circ}$.

IR spectrum (nujol mull): ν_{max} 3330 cm^{-1} (OH). PMR characteristics at 60 MHz in D_2O (DSS): 10 proton aromatic singlet, 451 Hz; $\underline{CH_2}Ph$, 4 proton broad singlet, 179 Hz; $-\underline{CH_2}-\underline{CH_2}-$, broad bands centred at 195 and 115 Hz; NMe_2 , singlet, 176 Hz.

Found: C, 71.54; H, 8.04; $C_{19}H_{25}NO.HCl$ requires: C, 71.34; H, 8.19%.

Acid-Catalysed Dehydration of 4-Dimethylamino-2-benzyl-1-phenylbutan-2-ol (138)

The tertiary alcohol (138) hydrochloride (12 g) was dissolved in a solution of concentrated HCl (75 ml) and acetic acid (150 ml) and the mixture heated under reflux for 6 hr. After cooling, the solution was poured onto ice and basified with strong aqueous ammonia before extraction of the aminoalkenic products into ether. Evaporation of the dried (Na_2SO_4) solution gave the basic products (9.4 g) whose PMR spectrum (CDCl_3 , TMS) showed three vinylic signals (394 and 385 Hz singlets and 333 Hz (J7) triplet) due to the presence of the cis and trans but-1-enes (140) and the but-2-ene (139) in approximately equal amounts (PMR integral data). Acidification of the product with ethanolic HCl and fractional crystallisation afforded:

4-dimethylamino-2-benzyl-1-phenylbut-2-ene (139) hydrochloride, (1.93 g), m.p. 201-202°. PMR characteristics at 60 MHz in CDCl_3 (TMS): $=\text{C}-\underline{\text{H}}$, triplet, 349 Hz (J7); $\underline{\text{CH}_2}\text{N}$, doublet of doublets, 228 Hz (J's 7 and 5); $\underline{\text{CH}_2}\text{Ph}$, broad singlets, 205.5 and 203 Hz; NMe_2 , doublet, 165 Hz (J_{NH}^+ 5).

Found: C, 75.62; H, 7.98. $\text{C}_{19}\text{H}_{23}\text{N} \cdot \text{HCl}$ requires: C, 75.58; H, 8.01%.

Also isolated was a 50:50 mixture (PMR integral data) of the cis and trans 4-dimethylamino-2-benzyl-1-phenylbut-1-ene (140) hydrochlorides, (5.7 g), m.p. 140-144°.

PMR characteristics at 60 MHz in CDCl_3 (TMS):
=C-H, broad singlets, 401 and 394 Hz; CH_2Ph , broad singlets, 220 and 212 Hz; $\text{CH}_2\text{CH}_2\text{N}^+$, broad singlets, 164.5 and 159 Hz; NMe₂, singlets, 155 and 149.5 Hz.

Treatment of the 4-Dimethylamino-2-benzyl-1-phenylbut-1-enes (140) with Potassium Permanganate

This reaction was carried out according to the method of Frey et al., (1950), as follows: the 50:50 mixed but-1-ene hydrochlorides (140), (5.0 g), were dissolved in water (100 ml) and the solution cooled to 5°. 1% aqueous potassium permanganate (400 ml) was then added dropwise over 30 min to the stirred mixture keeping the temperature in the 0 to 10° range and the mauve colouration was discharged after each addition. Stirring was continued at 0-10° for a further 1 hr after which the reaction mixture was allowed to warm to room temperature.

The suspension was then filtered free of MnO_2 and the filtrate was acidified with concentrated HCl (a strong smell of benzaldehyde was observed at this point). The benzaldehyde globules were extracted out of the acidic

phase with ether and the organic layer discarded. The aqueous mother liquor was then basified with ammonia and thoroughly extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal solution gave no trace of any product.

It was therefore deduced that further oxidation of the expected ketonic product (132), probably to phenylacetic acid, had occurred, and that this final oxidative product must have been present with the benzaldehyde in the discarded ethereal extracts obtained from the acidic phase.

EXPERIMENTAL WORK RELEVANT TO CHAPTER 5 - APPLICATION OF
THE PRINCIPLE OF THE ADDITIVITY OF SHIELDING EFFECTS IN
OLEFINIC COMPOUNDS FOR CONFIGURATIONAL ASSIGNMENTS IN
4-AMINO BUT-2-ENES

Preparation of 2,3-Diphenylprop-1-ene (144)

4-Dimethylamino-1,2-diphenylbutanol (29a) (12.3 g; 0.046 M) (see p. 255) was stirred with cyanogen bromide (4.2 g; 0.039 M) and sodium carbonate (7.5 g; 0.07 M) in chloroform (200 ml) for 3 hr at room temperature. The mixture was then heated under reflux for 13 hr before filtration via kieselguhr to remove the inorganic precipitate. The filtrate was washed with three 200 ml portions of 10% HCl (to remove basic impurities or unchanged amino-alcohol) and then with water after which the organic layer was separated and dried (Na_2SO_4). Evaporation to dryness gave the crude prop-1-ene product, (3.5 g; 40%). Distillation under reduced pressure led to the isolation of pure 2,3-diphenylprop-1-ene (144), b.p. $90-92^\circ/0.85$ mm (Cram and Hunter, 1964, gave b.p. $81-83^\circ/0.12$ mm).

UV spectrum: λ_{max} 243 m μ (ϵ 12550) (EtOH). PMR characteristics at 60 MHz in CDCl_3 (TMS): 10 proton aryl singlet, 432 Hz; $=\text{C}<\overset{\text{H}}{\underset{\text{H}}{\text{H}}}$, broad singlets, 327 and 299 Hz; CH_2Ph , broad singlet, 229 Hz.

The above chemical shifts agreed very well with the 60 MHz values calculated from Bumgardner's (1966)

100 Hz data (also in CDCl_3) for the same compound (10 proton aryl singlet, 432 Hz; vinylics, 327 and 300 Hz; CH_2Ph , 228 Hz).

Synthesis of trans-3-Dimethylamino-1-phenylprop-1-ene
(146)

Preparation of the Secondary Alcohol Precursor (145)

(a) The Mannich base (38), isolated from the hydrochloride (10.7 g; 0.05 M) was added dropwise to a suspension of lithium aluminium hydride (3.8 g; 0.1 M) in anhydrous ether (200 ml), over 15 minutes at a rate just sufficient to keep the reaction mixture gently on the boil. The suspension was refluxed for 1.5 hr and then stirred overnight at room temperature. Careful decomposition of the remaining lithium aluminium hydride with water produced an alumina gel from which the ethereal solution was decanted. The gel was washed several times with ether and the extracts were added to the mother liquor. Evaporation of the combined and dried (Na_2SO_4) ethereal solution gave the basic secondary alcohol product. The latter was acidified with ethanolic HCl and dilution of the solution with ether, followed by storage at 0° yielded pure 3-dimethylamino-1-phenylpropan-1-ol (145) hydrochloride, (7.0 g; 62%), m.p. 135° (Denton et al., 1949, gave m.p. $134-135^\circ$).

IR spectrum (nujol mull): ν_{max} 3270 cm^{-1} (OH).

(b) Acid-Catalysed Dehydration of the Alcohol (145)

The alcohol (4.0 g) was heated under reflux with concentrated HCl (20 ml) and acetic acid (35 ml) for 3 hr. The basic product was isolated in the normal way (NH_3 , ether) and acidification with ethanolic HCl afforded the trans-prop-1-ene (146) hydrochloride, (2.1 g), m.p. 190° (Holmes and King, 1947, gave m.p. $190-191^\circ$).

PMR characteristics at 60 MHz in CDCl_3 (TMS): 7 vinylic peaks at 419.5; 404, 397, 391, 384, 374, and 368 Hz; CH_2N , doublet of doublets, 230.5 Hz (J's 7 and 5); NMe_2 , doublet, 171 Hz (J_{NH}^+ 5).

Decoupled PMR characteristics at 100 MHz in CDCl_3 (TMS): Irradiation at the CH_2N frequency (386 Hz) allowed the vinylic protons to appear as an AB quartet with peaks at 647, 639, 626 and 618.5 Hz.

Preparation of 1-t-Butyl-3-dimethylaminopropan-1-ol (147)

The Mannich base (77), isolated from the hydrochloride (13.5 g; 0.07 M) was added dropwise with stirring to a suspension of lithium aluminium hydride (3.8 g; 0.01 M) in anhydrous ether (200 ml) at a rate which kept the mixture gently on the boil. The total time of addition was 25 min after which the mixture was heated under reflux for 3.5 hr. After cooling, the excess lithium aluminium hydride was carefully decomposed with water and the resulting gel was allowed to settle overnight. Decantation

and several ether washings of the gel allowed extraction of the product and subsequent evaporation to dryness of the solution gave the crude alcohol as a yellow oil. The latter was acidified with ethanolic HCl and after dilution of the solution with ether, the secondary alcohol product separated as the hydrochloride, (8.2 g; 60%), m.p. 159° (EtOH/ether).

IR spectrum (nujol mull): ν_{\max} 3450-3250 cm^{-1}
(bonded OH)

PMR characteristics at 60 MHz in CDCl_3 (TMS): -OH, broad singlet (which collapsed after the addition of a drop of D_2O), 223 Hz; NMe_2 , doublet, 174 Hz (J_{NH}^+ 5); $\text{CH}_2\text{CH}_2\text{N}$, centres of A_2X_2 multiplets, 201 and 111 Hz; t-Bu , singlet, 55 Hz.

Found: C, 55.16; H, 11.50. $\text{C}_9\text{H}_{21}\text{NO} \cdot \text{HCl}$ requires: C, 55.24; H, 11.33%.

Treatment of 1-t-Butyl-3-dimethylaminopropan-1-ol (147)
with an Acetic-Hydrochloric Acid Mixture

The alcohol hydrochloride (2.0 g) was dissolved in a mixture of concentrated HCl (20 ml) and acetic acid (35 ml) and the solution heated under reflux for 12 hr. The basic product was isolated in the normal manner and acidified with ethanolic HCl. Addition of ether and standing at 0° gave a crop of prisms consisting of the acetate ester hydrochloride (149) (0.16 g) of the alcohol substrate,

m.p. 207°.

IR spectrum (nujol mull): ν_{\max} 1720 cm^{-1} (C=O)

PMR characteristics at 60 MHz in CDCl_3 (TMS):

C-H, doublet of doublets, 280 Hz (J's 3.5 and 9); NMe_2 , doublet, 171 Hz (J_{NH}^+ 5); CH_2CH_2 , centres of broad bands, ca. 180 and 130 Hz; $\text{OC}-\text{Me}$, singlet, 126 Hz; t-Bu , singlet, 54.5 Hz.

Found: C, 55.81; H, 10.06. $\text{C}_{11}\text{H}_{23}\text{NO}_2 \cdot \text{HCl}$ requires: C, 55.55; H, 10.17%.

Treatment of the Alcohol (147) with Aqueous Sulphuric Acid Solutions of Varying Strength

(a) The alcohol hydrochloride (147) (1.84 g) was treated with 85% aqueous H_2SO_4 at 100-110° for 2 hr. A black solution was formed and after basification with strong ammonia and extraction with both ether and chloroform, no products were evident in either of the evaporated extracts. It was therefore concluded that oxidative decomposition had occurred.

(b) In two separate experiments, the alcohol hydrochloride (147) (1.2 g) was treated with 40% aqueous H_2SO_4 under reflux for 1.5 hr. Isolation and PMR examination (in CDCl_3) of the basic products showed breakdown of the t-Bu signal and the appearance of several overlapping peaks in the vinylic and aryl-Me resonance regions. In one experiment the acidified product yielded a crop of the unchanged

alcohol hydrochloride (0.16 g) (m.p., mixed m.p., and IR spectrum identical to authentic material).

These observations were interpreted as being due to the occurrence of Wagner-Meerwein carbonium ion rearrangements of the substrate under the reaction conditions.

Treatment of the Alcohol (147) with Phosphorus Pentachloride

The alcohol hydrochloride (147) (2.6 g) was intimately mixed with phosphorus pentachloride (3.0 g) and spontaneous reaction occurred to form a tarry solution. The latter was heated under reflux for 30 min before pouring onto ice and basifying the solution with strong ammonia. The emulsion was extracted with ether and evaporation of the separated and dried (Na_2SO_4) organic layer gave the basic products. PMR examination of the latter (in CDCl_3) again indicated the formation of Wagner-Meerwein rearrangement products (see previous experiment).

PMR Spectra of 3,3-Dimethylbut-1-ene (150)

The sample used in these experiments was an unpurified product obtained from the Aldrich Chemical Company.

60 MHz spectral characteristics in CDCl_3 (TMS): ABC vinylic pattern showed peaks at 368, 359, 350.5 and 340 Hz (H_C 'slanted' quartet) and also at 305, 303, 296.5, 294, 287, 285.5 and 284 Hz (AB overlapping area); t-Bu, singlet, 62 Hz.

100 MHz spectral characteristics in CDCl_3 (TMS):

ABC vinylic peaks (see Figure 15 of the main text);

t-Bu, singlet, 99 Hz.

EXPERIMENTAL WORK RELEVANT TO CHAPTER 6 - A GENERAL THEORY
FOR THE POSSIBLE STRUCTURAL AND CONFORMATIONAL REQUIREMENTS
OF HISTAMINE ANTAGONISTS

Only one compound was obtained for this Chapter of the thesis and this was 1-methyl-4-phenyltetrahydropyridine (164). This compound was kindly supplied by Dr. M.M.A. Hassan, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, who had prepared the sample by the method of Mansfield and Schmidle (1955).

EXPERIMENTAL WORK RELEVANT TO CHAPTER 7 - CONFORMATIONAL STUDIES OF HISTAMINE AND VARIOUS ANALOGUES AND ATTEMPTS TO INTRODUCE THE IMIDAZOLE NUCLEUS INTO AN ANTIHISTAMINIC STRUCTURE

Reductive Methylation of Histamine to form 4(5) (Dimethylaminoethyl)imidazole (169)

Histamine dihydrochloride (1) (2.00 g) (Ex Aldrich Chemicals) was dissolved in water (3 ml) before dilution of the solution with ethanol (125 ml). After the addition of formaldehyde (4 ml, 40% aqueous solution) and 10% palladised charcoal (0.5 g) the mixture was stirred with hydrogen at room temperature and atmospheric pressure until gas absorption ceased (1.5 hr required). The reaction mixture was filtered through keiselguhr and the filtrate evaporated to dryness under reduced pressure. Benzene (150 ml) was added to the residual syrup and the last remaining traces of moisture were removed by azeotropic distillation using a Dean-Stark head. Removal of the benzene solvent by rotary evaporation left the crude product as an oil. The latter was dissolved in a few ml of hot methanol and after the addition of methyl ethyl ketone until the solution was close to coalescence point, the pure dimethylamino hydrochloride derivative (169) (1.63 g; 70%), m.p. 186° (Huebner et al., 1949, gave m.p. 184°), separated out. A routine 60 MHz PMR spectrum of the hydrochloride

(see Table XX) was compatible with the structure of the product.

Preparation of 4(5)(Trimethylaminoethyl)imidazole iodide (170)

The dimethylamino (169) hydrochloride (0.42 g) derivative was suspended in ether (50 ml) containing 2 drops of water and after the addition of one pellet of sodium hydroxide the mixture (contained in a mortar) was vigorously triturated with a pestle. In this way, the free base of the substrate passed into the ether and sodium chloride solid began to appear. The ethereal solution was decanted off, dried (Na_2SO_4) and methyl iodide (0.15 ml) added to the filtered solution. After a few min the quaternary methiodide began to separate. Standing at 0° and several collections yielded the methiodide (170), (0.22 g; 40%), m.p. 236° (MeOH/ether).

Found: C, 34.20; H, 5.82. $\text{C}_8\text{H}_{16}\text{IN}_3$ requires: C, 34.17; H, 5.73%.

THE SYNTHESIS OF α -METHYL HISTAMINE (171) FROM L-HISTIDINE (168)

N.B. The characteristics of the routine 60 MHz PMR spectra of all the imidazole intermediates described below are given in Table XX of the main text.

Preparation of N-Benzoylhistidinol (186)

This three-stage synthesis was carried out (with some modifications) essentially by the methods of Adams et al., 1955; thus, a solution of L-histidine (168) monohydrochloride monohydrate (50.4 g; 0.24 M) (Ex Aldrich Chemicals) in 2N-sodium hydroxide (240 ml) was cooled to 5°, and then benzoyl chloride (37.2 ml; 0.32 M) and further 2-N sodium hydroxide solution (520 ml) contained in two separate dropping funnels, were simultaneously added to the substrate over 1.5 hr keeping the temperature of the mixture between 0 and 10° by vigorous stirring and cooling of the reaction flask in an ice-bath. When the addition was complete, the reaction mixture was stirred for a further 1.5 hr at 0 to 10° before being neutralized with concentrated HCl (85 ml) and glacial acetic acid (10 ml). After storage at 0° overnight, the product was filtered off, washing with cold water and ether (to remove unwanted benzoic acid) before being dried at 110° under reduced pressure (vacuum oven). The crude monobenzoyl-L-histidine (184) product (58.1 g; 93%), m.p. 240-242° (dec.) (Adams et al., gave m.p. 247°), was used for the next stage without purification.

Hence, the monobenzoyl derivative (184) (70 g; 0.27 M) was suspended in absolute methanol (700 ml) and after fitting the reaction flask with a gas inlet tube and a reflux condenser (protected by a CaCl₂ tube), dry HCl gas was bubbled

through the mixture (without cooling) over a period of 3 hr. The saturated solution was allowed to stand overnight at room temperature before the HCl and methanol were removed by evaporation under reduced pressure. The residue was dissolved in water (300 ml) before crushed ice and strong ammonia solution were added until the mixture was faintly ammoniacal. After storage at 0° the crystalline product separated and after collection was dried at 60° under reduced pressure (vacuum oven). The crude methyl ester (185) product (53.5 g; 73%), m.p. 155-157° (Adams et al., gave m.p. 159°) showed a well resolved IR spectrum (see below) and was therefore used for the next reaction as obtained.

IR spectrum (nujol mull): ν_{\max} 1750 cm^{-1} (C=O).

The last reaction of the three-stage sequence was considerably modified from the literature method after several experiments had yielded only about 30% of the reduced product (186). The amount of lithium aluminium hydride used was reduced and the alumina gel (formed during the latter stages of the reaction) was extracted with methanol to afford more product.

Thus, the ester (185) (30 g; 0.11 M) was suspended in anhydrous tetrahydrofuran (1000 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (12 g) in anhydrous ether (150 ml), keeping the reaction mixture gently on the boil. When the addition was complete, the

suspension was heated under reflux for 9 hr before cooling and carefully decomposing the excess hydride with water (25 ml). The mixture was stood overnight to allow the alumina gel to settle and then the organic phase was decanted off and concentration of the solution gave a crop of white crystals of the reduced product (186) (7.9 g), which were suspended in ice-water and filtered off.

A further 12.0g of the product was obtained by extraction of the gel with hot methanol. The cooled methanolic extracts were filtered via kieselguhr and concentration to dryness gave further product. Hence, the total yield of N-benzoyl histidinol (186), (19.9 g; 74%), m.p. 207-208^o (Adams et al., 1955, gave m.p. 210^o) was considerably improved by the gel extraction.

IR spectrum (nujol mull): ν_{\max} 3270 cm⁻¹ (OH). The product (186) formed a hydrobromide, m.p. 166^o (EtOH/ether).

Found: C, 47.90; H, 4.94. C₁₃H₁₅N₃O₂.HBr requires: C, 47.85; H, 4.94%.

Attempted Tosylations of N-Benzoyl-L-Histidinol (186)

(a) N-benzoyl histidinol (186) (1.23 g) and p-toluene sulphonyl chloride (tosyl chloride) (0.95 g) were suspended in water (100 ml) containing potassium carbonate (1 g), and the mixture heated under reflux for 15 hr. Thorough extraction with ether and concentration of the extracts

to dryness gave the unchanged substrate, (0.50 g), m.p. mixed m.p., and IR spectrum identical to those of authentic material.

(b) N-Benzoyl histidinol (186) (1.23 g) was stirred with tosyl chloride (1.04 g) in N/5 NaOH solution (100 ml) at room temperature for 12 hr and then at 60° for 3 hr. After standing for 2 days at room temperature the unchanged substrate (0.55 g) separated out (IR spectrum identical to that of authentic material).

(c) N-Benzoyl histidinol (186) (1.23 g) was suspended in pyridine (50 ml) and after addition of tosyl chloride (1.04 g), dissolution of the substrate occurred. The reaction solution was stored at 0° for 120 hr (following the methods of Mikhail and Portoghese, 1966, and Schleyer 1967), after which the pyridine solvent was removed under reduced pressure. The residual tar was dissolved in chloroform (100 ml) and the solution washed several times with dilute sodium hydroxide. The dried (K_2CO_3) chloroform extract was then concentrated down to dryness and a crystalline sample of the N-benzoyl histidinol substrate (0.25 g) was isolated (IR spectrum identical to that of authentic material).

Attempted Preparations of the Chloromethyl Intermediate (188)

(a) N-benzoyl histidinol (186) (1.0 g) was heated under reflux with thionyl chloride (25 ml) for 3 hr. Removal of unchanged thionyl chloride under reduced pressure left an

intractable tar.

(b) N-Benzoyl histidinol (186) (2.42 g) was suspended in chloroform (100 ml) and fresh thionyl chloride added (2.0 ml) which effected the dissolution of the substrate and the evolution of heat. The reaction mixture was heated under reflux for 6.5 hr and after cooling, the buff precipitate (m.p. 185-188^o) (2.8 g) was filtered off, washing with chloroform. A PMR spectrum of this product (in DMSO-d₆) was identical to that of authentic N-benzoyl histidinol hydrobromide (see Table XX) which suggested that it was the hydrochloride salt of the unchanged substrate.

(c) N-Benzoyl histidinol (186) (2.5 g) was heated under reflux with phosphorus oxychloride (20 ml) for 5 hr. The oxychloride and other volatiles were removed under reduced pressure to leave a bituminous material which proved intractable.

(d) N-Benzoyl histidinol (186) (0.5 g) was heated under reflux with phosphorus pentachloride (0.5 g) for 30 min. Pouring onto ice gave yet another intractable tar.

Preparation of Histidinol Dihydrochloride (193)

The literature method of Adams et al. (1955) was followed exactly; thus, N-benzoyl histidinol (10 g) was heated under reflux with 5-N HCl (150 ml) for 2 hr. The cooled solution was extracted free of benzoic acid using

ether, and concentration of the aqueous layer to a small volume afforded the crystalline product (after scratching and the addition of a little ether). The dihydrochloride (193) (6.86 g; 79%) had m.p. 197-198^o (EtOH/ether) (Adams et al., 1955, gave m.p. 198^o).

Treatment of L-Histidinol (193) with a 32% Solution of Hydrobromic Acid in Acetic Acid

(a) (L)-Histidinol dihydrochloride (193) (4.5 g) was dissolved in a few drops of strong aqueous ammonia contained in a 200 ml pressure bottle (Fisher Scientific Company) and a 32% solution of HBr in acetic acid (75 ml) (Ex Eastman Organic Chemicals) (obtained from a freshly opened bottle) was added. The sealed vessel was then heated at 110-120^o (oil-bath) with internal magnetic stirring for 36 hr. After cooling, the bottle was carefully opened and the solution concentrated down to dryness under reduced pressure. A 50:50 ether/hexane solution was added to the residual oil and white leaflets of the unchanged histidinol (193) dihydrobromide substrate (4.86 g), m.p. 185-186^o, separated out (PMR and IR spectra identical to those of the dihydrochloride).

Found: C, 23.67; H, 4.06. $C_6H_{11}N_3O \cdot 2HBr$ requires: C, 23.79; H, 4.32%.

(b) L-Histidinol dihydrobromide (193) (1.80 g) was dissolved in an aged solution of 32% of HBr in acetic acid

(40 ml) (Ex Eastman Organic Chemicals) (red-brown in colour) and heated at 110-120° (oil-bath) in a pressure bottle for 19 hr. After cooling, the solution was concentrated down to dryness and an oily red-brown solid formed the residue. Trituration of the latter with ethanol gave α -bromomethyl histamine (194) dihydrobromide, (1.86 g), m.p. 214-215° (EtOH/ether).

Found: C, 20.05; H, 3.28. $C_6H_{11}N_3 \cdot 2HBr$ requires: C, 19.69; H, 3.31%.

Hydrogenolysis of α -Bromomethyl Histamine (194) to form α -Methyl Histamine (171)

Initially, several attempts to hydrogenolyse the bromo derivative (194) using Pd/C (in ethanol) or PtO_2 (in ethanol or methanol) failed, with only unchanged starting material being recovered (IR and m.p. evidence).

Successful reduction was achieved using Barrow and Fergusons' method (1935); thus, α -bromomethyl histamine dihydrobromide (194) (0.40 g) was dissolved in a solution of sodium acetate (0.5 g) in 10% aqueous acetic acid (25 ml) containing 10% palladised charcoal (0.5 g). The mixture was hydrogenated at room temperature and pressure until gas absorption had ceased (18 hr required) and the filtered solution was concentrated down to dryness. The residual solid was extracted with hot ethanol and the organic solution evaporated to dryness to yield a pink and oily solid.

The latter was triturated with anhydrous ether to afford a buff solid (0.51 g), m.p. 110-115°. A PMR spectrum of the product in D₂O (see Table XX) showed a high-field secondary Me doublet which clearly established the presence of the required α -Me histamine (171). However, sodium acetate was also present (showing a sharp Me singlet at 120 Hz). Several recrystallisation attempts from EtOH/ether failed to remove the inorganic impurity. Release of the free base by addition of ammonia gave an aqueous solution from which the α -Me histamine could not be extracted (CHCl₃, ether) even after saturation with NaCl, which suggested that the base is infinitely soluble in water.

In a repeat experiment using 0.50 g of the dihydrobromide substrate (194) another ammoniacal solution of α -Me histamine was obtained, and treatment of the solution with aqueous picric acid led to the isolation of a pure sample of the product as the dipicrate, (0.39 g), m.p. 182-183° (H₂O) (Alles et al., 1957, isolated a dipicrate monohydrate, m.p. 202-204°).

IR spectrum (nujol mull): ν_{\max} OH (absent)

Found: C, 37.06; H, 2.94; N, 21.54. C₁₈H₁₇N₉O₁₄ requires: C, 37.06; H, 2.94; N, 21.61%.

ATTEMPTS TO INTRODUCE THE IMIDAZOLE NUCLEUS INTO AN
ANTI-HISTAMINIC STRUCTURE

Preparation of the 2-Lithio-1-methylimidazole (201)
Complex and its Reaction with Cyclohexanone

(a) Initially, the complex was prepared according to the method of Roe (1965); thus, an ethereal solution of n-BuLi was prepared by Akhtar and Barton's method (1964) (see p.276) using n-butyl bromide (17.8 g; 0.13 M) and lithium (1.81 g; 0.26 g atom). 1-Methylimidazole (6.6g) (Ex Aldrich Chemicals) in anhydrous ether (100 ml) was added dropwise to the n-BuLi solution (at 0 to 10°) and the mixture allowed to warm at room temperature before stirring for 1.5 hr. The yellow suspension was then cooled to 0° and cyclohexanone (7.85 g; 0.08M) added, after which the mixture was stirred at room temperature for 5.5 hr. The complex was decomposed by pouring onto crushed ice and dilute HCl and the ethereal layer discarded. The aqueous layer was basified with strong ammonia solution and the basic product extracted into ether and dried (Na₂SO₄). Evaporation of the organic solution gave the crude 1-(1-methylimidazol-2-yl)cyclohexanol (204) product, (0.55 g; 4%), m.p. 175° (Roe, 1965, gave m.p. 177-178°).

(b) The very poor yield obtained from the previous reaction was greatly improved by refluxing the n-BuLi and 1-methylimidazole mixture for 3 hr instead of stirring at room

temperature. In this way, a repeat reaction carried out on the same scale gave 7.48 g (52%) of the product (204).

Attempted Reaction of the 2-Lithio-1-methylimidazole Complex (201) with Two Mannich Ketones

(a) The lithio complex (201) was prepared by the improved method described above using n-butyl bromide (23.3 g; 0.17 M), lithium (2.35 g; 0.34 g atom), 1-methylimidazole (12.0 g; 0.15 M) and anhydrous ether (200 ml). A solution of the phenyl Mannich base (38) in ether (50 ml) isolated from the hydrochloride (31.2 g; 0.15 M) was added dropwise and the mixture stirred at room temperature for 3 hr. After pouring onto crushed ice and ammonium chloride, the ethereal layer was separated and dried (Na_2SO_4). Evaporation of the organic phase yielded 23.2 g of the unchanged ketone starting material (IR and PMR spectra identical to those obtained from authentic material).

The aqueous phase was then further extracted using chloroform and concentration to dryness of the extracts afforded 11.0 g of the 1-methylimidazole starting material (IR and PMR spectra identical to those obtained from authentic material).

(b) The lithio complex (201) was prepared from n-butyl bromide (10.0 g; 0.073 M), lithium (1.02 g; 0.146 g atom), 1-methylimidazole (4.8 g; 0.06 M) and anhydrous ether

(200 ml). Reaction with the p-tolyl Mannich base (103) (0.047 M) and work-up as before gave 6.9 g of the unchanged ketone substrate (103) after the ether extraction.

Hence, no detectable reaction had occurred in either of the two reactions of the lithio complex (201) with the Mannich ketones (38 and 103).

Reaction of the 2-Lithio-1-methylimidazole Complex (201) with N-Phenethyl-4-piperidone (205)

The lithio complex (201) was prepared as before using n-butyl bromide (11.5 g; 0.084 M), lithium (1.2 g; 0.17 g atom), 1-methylimidazole (6.6 g; 0.08 M) and anhydrous ether (200 ml). 1-Phenethyl-4-piperidone (205) (15.0 g; 0.074 M) (kindly supplied by Dr. M.M.A. Hassan, University of Alberta) dissolved in dry benzene (250 ml) was added dropwise and the mixture stirred overnight at room temperature. The complex was decomposed with crushed ice and the organic layer separated and dried (MgSO_4). Evaporation to dryness yielded a brown semi-solid which was dissolved in ethanol and acidified with a stream of HCl gas. After addition of ether a crop of the ethyl ketal hydrochloride, (2.5 g), m.p. 179° (Beckett et al., 1959, gave m.p. $178-179^\circ$) separated out (this side product must have been formed by the action of ethanolic HCl on unchanged N-phenethyl-4-piperidone starting material).

The free base was then isolated from the mother liquor and evaporation of the ethereal extracts gave the 4-(1-methylimidazol-2-yl)-1-phenethylpiperidin-4-ol (201), (3.6 g; 11%), m.p. 196-197° (hexane).

Found: C, 71.21; H, 7.99. $C_{17}H_{23}N_2O$ requires: C, 71.55; H, 8.13%.

The product formed a dihydrochloride monohydrate, m.p. 207-208° (EtOH/ether).

IR spectrum (nujol mull): ν_{\max} 3500 cm^{-1} (H_2O).

Found: C, 53.85; H, 7.68. $C_{17}H_{23}N_3O \cdot 2HCl \cdot H_2O$ requires: C, 54.24; H, 7.23%.

Attempts to Dehydrate 1-(1-Methylimidazol-2-yl)cyclohexanol
(204)

(a) The alcohol (204) (3.0 g) was heated under reflux with a mixture of hydrochloric (25 ml) and acetic acids (50 ml) for 3 hr. Isolation of the base in the usual way yielded the unchanged alcohol substrate (204) (1.9 g) (m.p. and mixed m.p. identical to that of authentic material).

(b) The alcohol (204) (1.5 g) was heated at 110-120° (oil-bath) in a solution of 85% H_2SO_4 (50 ml) for 3 hr. The reaction mixture was poured onto crushed ice and after basification with strong aqueous ammonia an intractable tar was obtained. It was therefore deduced that oxidative decomposition of the alcohol had occurred.

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B29945